New Orleans Medical
and
Surgical Journal

Vol. 100 NOVEMBER, 1947 No. 5

CIRCUMVALLATE PLACENTA*

ARTHUR B. HUNT, M. D.†
ROBERT D. MUSSEY, M. D.†
AND
JOHN E. FABER, M. D.†
ROCHESTER, MINN.

The subject of circumvallate placenta does not appear frequently in the obstetric literature. One of us (A.B.H.), who previously had become interested in this subject through the suggestion of W. J. Dieckmann, discussed it in 1935 and reported two cases.[1] Since then, our interest in this subject has prompted closer inspection of placentas and has led to the collection of additional data, particularly of data relating to clinical symptoms and fetal mortality.

In approximately half of the instances of circumvallate placenta that we have observed, the symptoms somewhat resembled those of placenta previa or of premature separation of the placenta. We, therefore, feel that it is worthwhile at this time to compare the symptoms of these three conditions. In several instances, circumvallate placenta occurred in more than one pregnancy in the same case. Its co-occurrence with placenta previa also has been noted.

Circumvallate placenta is an anomaly which has been of interest to obstetricians chiefly from anatomic and pathologic viewpoints. Williams,[2] Goodall[3] and others have written complete descriptions of this anomaly, have cited the theories of other authors as to its formation and have advanced their own plausible theories for its pathogenesis. Williams[2] quoted various German writers, notably Herff, Bayer, Seitz and others, who said that obstetric complications, such as abortion, unexplained bleeding, premature labor and anomalies of the third stage of labor, may result from circumvallate placenta. However, both Williams and Schumann stated that in their experience the anomaly had no clinical significance. On the contrary, Hobbs and Rollins[4] who, in 1934, reviewed their observations in 79 cases of this condition in a period of 13 years found that obstetric complications were present in 39 of the cases. The fetal mortality rate in their series was 43 per cent, which is higher than that for most obstetric conditions except perhaps for abruptio placentae, severe toxemia and rare instances of rupture of the uterus.

We shall review briefly the derivation of the term "circumvallate placenta," the probable pathogenesis of the condition and the anomalous structure to which its symptoms appear to be related. It will be recalled that the entire surface of the embedded amniotic sac is covered with villi which exhibit a profuse growth usually in the area most closely approximated to the uterine wall. As the placenta develops, that portion of the chorion which overlies this profuse growth is called the "chorion frondosum" while the part of the chorion from which the villi have atrophied and disappeared is called the "chorion laeve." The chorion frondosum has a smooth glistening fetal surface which is called the "placental plate."

*Read before the sixty-seventh meeting of the Louisiana State Medical Society, New Orleans, Louisiana, May 13-15, 1947.

†From the Section on Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota.

The placental plate has definite limits, the extent of which is determined by several factors which will not be considered here. The normal growth of the chorionic placental plate is determined usually by the size of the placental site, which in turn is related to the growth of the uterus and its contents.

The life cycle of the placenta covers a scant nine months. In the course of this time, as Goodall has aptly stated, the placental growth encompasses a life time—childhood, adolescence, maturity and senility. In some placentas, as in tissues of the body, degenerative changes may occur relatively early. In fact, infarction and sclerotic changes, which may appear early in gestation along the border of the placental plate, tend to interfere with the blood supply so that growth of the placental plate cannot keep pace with the increase in size of the growing placental site. In such cases, an outgrowth of villi may extend beneath and beyond the border of the chorion frondosum as an expression or attempt on the part of the placenta to maintain its function of nourishing the fetus. This outgrowth of villi causes them to pile up beyond the limits of the chorion frondosum and here they are covered by the chorion laeve, which is thus raised up from the wall of the uterus and put under tension by the vigorously growing villi. As this piling up of villi occurs outside the more or less fibrous limit of the chorion frondosum or placental plate, it may partially or completely surround the circumference of the placental plate with a mass of villi which is elevated above the level of the plate and gives rise to the term "circumvallate." It is along this circumference that the increasing tension may cause a tear in the tissue and produce bleeding and sometimes seepage of amniotic fluid.

INCIDENCE

Forty-seven instances of circumvallate placenta were observed among 8,861 consecutive deliveries on the service of the Section on Obstetrics and Gynecology of the Mayo Clinic from January 1, 1934 to December 31, 1946, inclusive. Prior to January 1, 1934, we had not always been alert to observe and record cases in which this anomaly was present and it is quite probable that some instances may have been overlooked since that date and that many more than 47 instances actually occurred. However, it is probable that the condition of the placenta was noted in all cases in which symptoms were produced. This supposition is strengthened by Hobbs and Rollins[4] who reported finding this anomaly in 79 cases. In only 45 of these cases was the pregnancy at or near term. Hobbs and Rollins also noted a ratio of one instance of circumvallate placenta in 50 pregnancies while we recorded one in 188 pregnancies.

In 23 of the 47 instances, the anomaly did not produce any clinical symptoms. These 23 instances of the anomaly occurred in 22 cases. The 24 instances of the anomaly which produced symptoms occurred in 19 cases; two instances of the anomaly occurred in each of three cases and three instances occurred in one case.

In standard textbooks on obstetrics, scant mention, if any, is made of the clinical importance of circumvallate placenta. This may be due to the fact that the anomaly frequently does not produce any symptoms that are of clinical importance. As we have just stated, there were no important symptoms in 23 of the 47 instances of this anomaly observed at the clinic. In these 23 instances, the duration of gestation averaged 39 weeks and a fetal death occurred in only one instance. In this instance, the fetus died three weeks before delivery. A history of bleeding was obtained in only two of the 23 instances. In each of these two instances, the bleeding occurred prior to the fourth month of gestation. On the other hand, in 15 of the 25 instances in which the anomaly produced symptoms that were considered important clinically, bleeding or spotting with blood or drainage of fluid occurred before the fourth month of gestation.

In nine instances, including some of those in which early bleeding persisted or recurred, uterine bleeding occurred in the last half of pregnancy. In seven instances the bleeding was due to circumvallate placenta,

while in two instances placenta previa also was present. In these two instances, the placenta previa was undoubtedly of greater importance clinically. Placenta previa is encountered in approximately one of every 200 pregnancies. Since it occurred in two of the 47 instances of circumvallate placenta, one may question whether some factor affecting nidation may not be an etiologic factor in both conditions.

In five of the seven instances just mentioned, the bleeding was of such severity, grade 2 to grade 3 (on the basis of 1 to 4) that it was thought, in the prepartum period, to be caused by premature separation of the placenta.

In 15 instances, the amniotic sac ruptured spontaneously preceding the onset of labor. In the majority of these instances, it ruptured before the thirty-fourth week of gestation; in seven instances, fluid (hydrorrhea gravidarum) drained for from one to ten weeks prior to the onset of labor, which in each instance was premature. Examination of the placenta indicated that, in all probability, tearing occurred at the fibrous ring which marks the border of the chorion frondosum or placental plate and that this was caused by the continuing growth of placenta while the insertion of the membranes remained stationary.

Rupture of the membranes preceding the onset of labor, which occurred in 15 or a third of the 47 instances, or in three-fifths of the instances in which symptoms were present, is of distinct clinical importance because it usually is followed by premature labor and commonly by death of the prematurely born infant.

In the 24 instances in which the circumvallate placenta produced symptoms, the fetal mortality was 50 per cent. The mortality was chiefly attributable to prematurity although some extremely premature babies survived as indicated in table 1. The fetal mortality rate in the 47 instances was 24 per cent. There were no maternal deaths although one patient (who did not have placenta previa) required a transfusion of blood.

TABLE 1

ONSET OF LABOR AND FETAL SURVIVAL IN TWENTY-TWO INSTANCES OF CIRCUMVALLATE PLACENTA WITH CLINCAL SYMPTOMS*

Onset of labor, weeks	Instances	Fetal survival
20 to 24	3	0
25 to 29	5	0
30 to 34	5	2
35 to 38	5	5
39 to 40	4	4
Total	22*	11 (50 per cent)†

*Two instances in which placenta previa was associated with circumvallate placenta have been excluded from this table.

†The fetal survival rate in the entire 47 instances of circumvallate placenta was 74 per cent.

When uterine bleeding occurs during pregnancy, it is necessary to determine, if possible, the cause of the bleeding, and it is especially important to rule out the more serious causes of maternal hemorrhage, that is, placenta previa and abruptio placentae. This usually can be done readily by the history and by careful physical and roentgenologic examination. Roentgenologic examination has not proved to be of accurate value before the eighth month of gestation. Table 2 shows the distinguishing features of circumvallate placenta and placenta previa, and table 3 shows the distinguishing

Table 2

DIAGNOSTIC FEATURES OF CIRCUMVALLATE PLACENTA AND PLACENTA PREVIA

Circumvallate placenta	Placenta previa
Bleeding prior to viability is not uncommon.	Bleeding more common after period of viability.
Bleeding usually slight and often accompanied by uterine contractions.	Bleeding often profuse, recurring and painless.
Seepage of amniotic fluid may occur.	No seepage of amniotic fluid.
Vaginal examination does not aid in the diagnosis.	Vaginal examination may disclose positive findings.
Roentgenologic examinations, including placentograms, do not reveal any abnormality.	Roentgenologic examinations, including placentograms, may disclose positive findings after the seventh month.

TABLE 3

DIAGNOSTIC FEATURES OF CIRCUMVALLATE PLACENTA AND PREMATURE SEPARATION OF PLACENTA

Circumvallate placenta	Premature separation of placenta
Hemorrhage is evident.	Hemorrhage is commonly concealed.
Shock is not present.	Shock may be present.
Uterus relaxes between contractions.	Toxic uterine contractions
Toxemia is unusual.	Toxemia is relatively common.
Bleeding prior to viability is not uncommon.	Hemorrhage more likely to occur in course of period of viability.
	Evidence of fetal distress or death.

features of circumvallate placenta and abruptio placentae. In several instances, it was impossible to distinguish between partial premature separation of the placenta and circumvallate placenta until the placenta was inspected.

MANAGEMENT

Only scant comment can be made concerning the management of this condition because only a presumptive diagnosis can be made until the placenta can be inspected. In a case in which hydrorrhea gravidarum develops, an effort should be made to prevent infection by the daily instillation into the vagina of one of the newer nonirritating, liquid antiseptics.

The management of bleeding during pregnancy, in the absence of evidence which will permit a positive diagnosis of placenta previa or of abruptio placentae, is one of expectancy. This requires great patience on the part of both the patient and physician. The patient must remain in bed, perhaps for many weeks, and the physician must have the forbearance to defer operative methods of delivery, such as cesarean section, unless symptoms indicate that this method of delivery is urgent.

COMMENT

One or more of the following signs or symptoms were observed in 24 of 47 instances of circumvallate placenta: (1) signs of threatened, but not inevitable, abortion; in many instances these signs recurred or did not subside; (2) prolonged but seldom profuse vaginal bleeding; (3) intermittent uterine contractions, and (4) early rupture of the membranes with hydrorrhea followed eventually by premature labor, sometimes prior to the third trimester of pregnancy. If hydrorrhea is present, prognosis for the fetus is poor.

The maternal hazard is due to hemorrhage and potential infection. The hemorrhage is seldom profuse and no instance of death or even shock from hemorrhage occurred in the cases reported by Hobbs and Rollins.[4] Three patients in our series received blood transfusions; two of these also had placenta previa.

The danger of infection is potential because of the presence of blood in the lower part of the genital tract for a more or less prolonged period and because of the occasional (in ten instances of our series) prolonged period of time intervening between rupture of the membranes and labor. Postpartum fever occurred in two instances.

The fetal mortality was 24 per cent in the 47 instances of this anomaly. The anomaly was observed in 47 of 8,861 deliveries (1:188).

Repeated instances of circumvallate placenta in the same case have not been reported previously. We have observed five cases in which the anomaly occurred on more than one occasion. In four of these cases the anomaly was accompanied by symptoms of clinical importance. One of these patients had three deliveries each complicated by circumvallate placenta; all three babies survived, although two of them weighed only 1,270 and 1,360 gm. respectively. Two of the mothers, who each had this complication on two occasions, lost the infants prematurely. Almost all of the women who had a recurrence of circumvallate placenta had other pregnancies which were not complicated by this anomaly and a majority of the women who had only one pregnancy that was complicated by this anomaly had other uncomplicated pregnancies and gave birth to living children at full term. It is evident that there is a definite tendency toward the recurrence of circumvallate placenta which occurred nine times among four of the 19 patients who had clinical symptoms.

Circumvallate placenta is probably one of the few known etiologic factors in the condition known as hydrorrhea gravidarum, although it does not explain all instances of this condition, especially those in which the pregnancy proceeds to term. Circumvallate placenta is an obstetric entity of definite fetal and some maternal significance which should be kept in mind when one is confronted with unaccountable bleeding in the course of pregnancy. The frequency of the occurrence of circumvallate placenta and the fetal hazard of this condi-

tion are not generally appreciated. Conservative management of protracted slight bleeding or of hydrorrhea during pregnancy requires great patience on the part of the patient, her relatives and the physician. In a number of instances, patience has been rewarded by the survival of a prematurely born infant.

DISCUSSION

Dr. J. S. Hebert (New Orleans): Dr. Mussey has given us a complete and most interesting paper on circumvallate placenta. Certainly I did not mean to say any more, except to thank him for such a valuable report. However, I would like to report a case in which two important points in his paper are brought out. First, severe hemorrhage does complicate the clinical course of a pregnancy to the extent of fatalities in babies. Second, the condition may be repeated.

In 1924 a first pregnancy resulted in a term spontaneous delivery of a normal healthy baby. In a second pregnancy, in 1926, resulted in a term spontaeous delivery of a normal healthy baby. In 1929 a third pregnancy resulted in a complete six weeks' spontaneous abortion. In 1930 a fourth pregnancy was normal until the eighth week, when bleeding started; the bleeding continued through the twenty-fourth week; patient remained more or less in bed these sixteen weeks. From then on to term ths pregnancy ran a normal course and resulted in term spontaneous delivery. This fourth pregnancy furnished the complete circumvallate placenta reported by Dr. Deeves in 1930. Then in 1933, a fifth pregnancy resulted in a complete eight week spontaneous abortion. In 1936 a sixth pregnancy ran a normal course until the eighth or ninth week, when bleeding started. This bleeding ran through the fifteenth week, when it stopped. Bleeding then began again about the thirty-second week and was so severe that it resulted in a premature spontaneous delivery. This child did not live. This placenta, though not complete, was of the circumvallate formation. In 1939 a seventh pregnancy resulted in a term spontaneous delivery of a normal healthy child. In 1944, for the eighth pregnancy which had been referred to one of my confreres, bleeding started about the eighth week, the hemorrhage continued and became so severe that pregnancy was terminated about the twenty-fourth week. No report on placenta was made.

Dr. Beacham (New Orleans): I am sure that I express the opinion of everyone here when I state that we are very grateful to Dr. Mussey for taking his valuable time to make a trip to New Orleans to speak to us on this important subject. In the future we will be on the lookout for these cases, and I hope within the next few years we can report to him that we have achieved the degree of accuracy of diagnosis which his group has attained.

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CHRONIC PENUMONIAS*

SYDNEY JACOBS, M. D.†
NEW ORLEANS

Although bronchiectasis, atelectasis and lung abscess are well-recognized entities, chronic non-specific pneumonias have not been given as much attention in medical literature as their frequency warrants. These chronic pulmonary inflammations are distinguished from ordinary acute pneumonia by massive exudation into the alveoli[1] followed by organization, suppuration and fibrosis.

Such chronic pulmonary inflammations are marked by exacerbations of cough and expectoration, chills and fever, dyspnea and thoracic pain alternating with periods of relative freedom from symptoms. The onset may be explosively acute as in pneumococcal pneumonia or insidious with few systemic symptoms as in the series of cases reported by Rich and Hamman.[2] In their patients, all the pulmonary interstitial tissues were hyperplastic and the alveolar walls tremendously thickened. Connective tissue proliferation within the alveolar walls compressed the capillary circulation of the alveoli and (independent of alveolar exudate) lead to progressive pulmonary fibrosis, increased pressure in the pulmonary artery and to right ventricular hypertrophy with congestive heart failure as a terminal phenomenon.

At times a definite etiology can be established in these cases by obtaining from the

*Read before a meeting of the Orleans Parish Medical Society, April 14, 1947.

†From the Department of Medicine, Tulane University School of Medicine, New Orleans.

sputum a pure culture of staphylococcus,[5] streptococcus or Friedlander's bacillus[3] or by postmorten isolation of an irritating lipid[4] from the lung. More often than not the exact cause is not determined because sputum studies are inconclusive, the flora apparently varying from day to day. Since the time of Laennec (1826) controversy has centered about these chronic pneumonias. Do they arise insidiously as chronic states or do they begin with acute phases? Often, one cannot answer this question satisfactorily.

The most impressive symptoms are dyspnea and bronchospasm so severe that very often the diagnosis of bronchial asthma is made, but the history is not the characteristic one of allergy. Rather it is one of repeated episodes of respiratory tract illnesses of varying severity. At times, it is difficult to eliminate congestive heart failure as the cause of symptoms. Differential venous pressures may be of assistance but frequently one must resort to a trial of digitalis which seldom helps these patients unless congestive heart failure has actually resulted from the massive pulmonary destruction. Generally this syndrome is established in middle life, and these patients are invariably "sickly" and underweight. Even in remission, there is pronounced lowering of respiratory reserve. Usually the roentgenogram indicates that the more centrally situated portions of the lung are consolidated and the more peripheral segments emphysematous. As Davison has pointed out, these cases do not fall clearly into the classification of bronchiectasis or lung abscess. A minor degree of bronchial damage[8] and bronchiectasis can be demonstrated by the pathologist postmorten or by the bronchoscopist antemortem, but the preponderant damage is to the lung parenchyme.

Not infrequently this syndrome results from organization of an unresolved pneumonia which apparently had begun as any other acute pneumonia. During ordinary bacterial pneumonia, a considerable amount of exudate is deposited in the alveoli; if it cannot be resolved by digestion and resorption, organization and fibrosis occur. Inasmuch as it can be produced experimentally either by leaving an excess of serum in the alveoli or by impeding lymphatic drainage, it is presumed that whatever blocks drainage (as by a mixed infection, pneumonia or by anthracosis[6]) may result in the analogous phenomenon clinically. Granulation tissue from various points on the alveolar walls gradually replaces the alveolar exudate and fills the alveoli with a contracted, dense, nearly airless mass of connective tissue. If there is additionally an empyema not speedily corrected, there will also occur shrinking and distortion of the hemithorax;[7] the trachea, heart and mediastinum are drawn to the affected side, the diaphram is elevated, and the chest wall markedly retracted. This lessens the mobility of the entire thorax and greatly embarrasses respiration. When the antecedent pneumonia has been secondarily invaded by staphylococci or streptococci, multiple abscesses may honeycomb a lobe or even the entire lung and lead to further septic complications. At times cavities may be scattered among foci of organizing pneumonia.

It is highly probable that chronic pneumonia will some day be recognized as an industrial hazard. In certain industries, notably those involving work with lacquers and shellacs, there is exposure to irritating lipids.[4] These contain fatty acids which injure the lung, the degree of destruction being proportional to the speed of hydrolysis and the amount of free acid released.

Inasmuch as the outlook for these patients is not good, and the treatment at best is symptomatic, it is essential to eliminate chronic fibroid tuberculosis, lung abscess, bronchiogenic carcinoma, bronchiectasis and allergic bronchial asthma for all of which definitive therapy is at hand. For patients with chronic pneumonias, treatment must be designed to enhance the natural resistance and to improve pulmonary ventilation.

During the exacerbation, complete bed rest is essential. Since there are undoubtedly many fresh foci of acute inflammation superimposed on the chronic substrate, opportunity must be afforded for a maximal

resolution of these. Oxygen by tent is usually necessary and bronchodilating drugs are needed. If these do not suffice, bronchoscopy will be required to free the bronchial tree of tenacious mucus. Antibiotic and sulfonamides sometimes seem to benefit, especially when inhalational methods are employed. Blood transfusions are usually indicated for the almost invariably concomitant anemia.

During the periods of remission, every effort should be made to favor bronchial drainage. Ventilation is at times enhanced by shrinking the nasal mucosa, while bronchial dilation is effected by aminophylline, epinephrine or ephedrine. Postural drainage and even repeated bronchoscopies may be required. Thinning of the sputum by expectorant cough agents is desirable, but the use of opiates to depress the cough reflex is injurious. In several European clinics, irradiation of the lungs has been practiced, but the tabulated results are not particularly impressive. It is to be emphasized that nutrition is to be maintained despite the patient's natural aversion to eating. As far as is practicable, the patient must be encouraged to conserve his respiratory efforts.

The prognosis is obviously poor. These people may live many years but they are seldom free of symptoms entirely. The course is progressively downward as the acute respiratory tract episodes tend to become more frequent and more severe. With the use of the newer chemotherapeutic agents, it is possible that the progress of the disease may to a considerable degree be slowed.

SUMMARY

The clinician encounters chronic pulmonary inflammations more often than is generally appreciated. The etiology may sometimes be established by examination of the sputum, but more often it cannot. The syndrome is featured chiefly by cough, lowering of respiratory reserve, intense dyspnea and marked weakness. The course is usually one of progressive debility, at times terminating in congestive heart failure. Treatment is designed to improve the patient's nutrition, to increase respiratory function by bronchodilatation and to combat bronchial infection by chemotherapy.

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DRUG REACTIONS AND THEIR TREATMENT, WITH SPECIAL REFERENCE TO THE USE OF BAL IN HEAVY METAL POISONING.*

C. BARRETT KENNEDY, M. D.†

AND

V. MEDD HENINGTON, M. D†.

NEW ORLEANS

Because of the abundance of material dealing with reactions to the newer drugs and because of the limited use of BAL in one practice, Dr. Henington and I have collaborated on this paper. Dr. Henington will present the reactions to benadryl and pyribenzamine, and I am covering the reactions to penicillin and the use of BAL in heavy metal poisoning.

It is not our purpose to detract from the unquestioned value of these drugs but merely to point out the limitations and,

*Read before the Sixty-seventh Annual Meeting of the Louisiana State Medical Society, New Orleans, May 14, 1947.

†From the Department of Dermatology, Louisiana State University School of Medicine.

under some circumstances, the actual dangers of their use.

PENICILLIN

I. Routes of administration:
  (1). Oral—
    (a). Tablets (25,000 units)
      (50,000 units)
      (100,000 units)
  (2). Parenteral—
    (a). Aqueous
    (b). In beeswax and peanut oil
  (3). Topical applications—
    (a). Aqueous
    (b). In water soluble ointment bases
  (4). Inhalation—atomizer sprays
  (5). Constant intravenous drip
  (6). Intrathecal

II. Reactions due to the drug itself:
  (1). Toxic erythema
    (a). First to third day of treatment.
    (a). Most often occurs after oral administration.
    (c). Manifested by generalized diffuse, fine, red, macular rash with pronounced subjective symptoms of itching.
    (d). Rash clears in seven to 10 days and is characterized by diffuse peeling.
  (2). Urticaria
    (a). Occurs within seven to 14 days after exposure to drug.
    (b). May follow all types of internal medication. The incidence of urticaria following the use of penicillin in beeswax and peanut oil is about 5 per cent,[1] no greater than that following aqueous solutions or oral medication. After beeswax and peanut oil injection, local reactions consisting of painful swelling and urticaria-like wheals surrounding the site of injection are quite common but of little consequence.
    (c). The urticarias are slight to severe with angioneurotic edema and sometimes with arthralgia.

Our findings are in accord with the conclusions of Pillsbury[2] and his associates, who report:

    (a). Reactions are more frequently encountered in patients who have had repeated courses of this drug.
    (b). The incidence of urticaria is increasing, being 1.8 per cent in 1944 and 5 per cent in 1946.
    (c). Readministration of the drug after severe urticarial reaction may or may not be followed by recurrence of the urticaria on reinjection of a full therapeutic dose of penicillin.
    (d). It is sometimes possible to continue penicillin therapy in a reacting patient by the simultaneous administration of an antihistamine drug.
    (e). Skin tests are unreliable.
    (f). Antihistamine drugs are particularly useful in controlling reactions.
  (3). The fungus dermatophytiid-like reactions
    (a). Early in the course of the therapy.
    (b). Patient who has had an "almost forgotten" Jock-strap itch which recurs during the injections of penicillin and clears up in a few days after medication has been discontinued.
    (c). Vesicular "dermatophytiid" eruption of hands and feet characterized by deep seated blisters along the sides of the fingers and toes. This clears up within a few days after medication has been discontinued.
  (4). Reactions following topical use on the skin
    (a). Often occurs in nurses.

(b). Incidence of allergic reactions is high.

(c). Local reaction is typical of dermatitis venenata.

(d). Subsequent internal medication may flare up a previously sensitized skin area.

(5). Intrathecal

(a). Immediate reactions of headache and nausea.

(b). Convulsions occur usually in single doses of over 100,000 units.[3, 4, 5]

(6). Reactions in syphilitic patients: The Herxheimer reaction and the therapeutic paradox

(a). Early syphilis (primary, secondary, asymptomatic with history under two years).

(1). Herxheimer reaction occurs in 35 to 50 per cent of all cases.

(a). Manifested by fever, chills, malaise, accentuation or precipitation of secondary rash, edema, or relapse of primary.

(b). If fever occurs during penicillin therapy, syphilis should be suspected in that individual.

(c). Treatment should *never* be discontinued because of this.

(b). Congenital syphilis

(1). Fifty per cent have Herxheimer reactions which consist of sharp elevations in temperature which do not appear to be injurious to the child.[6]

(2). Fatalities have been reported in premature malnourished infants.[7]

(3). Pediatricians are in general agreement that the gradual building up of the dosage is unnecessary in these cases.

(c). Syphilis and pregnancy

(1). Incidence of abortion is no higher during penicillin treatment of the mother than during other forms of antisyphilitic treatment.

(2). Incidence of abortion is no higher than the expected incidence of abortion in normal women.[8]

(d). Cardiac syphilis

(1). Because of the always potent danger of a Herxheimer reaction in cardiovascular syphilis, it is felt that these cases should always either:

(a). Receive prolonged preliminary courses of bismuth (two months) and iodides, or

(b). Twenty-four injections of 5,000 units at three hour intervals followed by 180 injections at 50,000 units.

(e). Central nervous system syphilis

(1). Asymptomatic. Herxheimer reactions not of serious import.

(2). Acute syphilitic meningitis. Herxheimer reaction not of serious import.

(3). Paresis and tabes dorsalis with or without optic atrophy. That these cases require special care can best be

illustrated by the following cases:

CASE NO. 1

41 year old male with proved central nervous system syphilis manifested by blurred vision, optic atrophy, and an Argyll Robertson pupil, entered the hospital for combined penicillin and malarial therapy. Penicillin therapy was begun at the rate of 50,000 units every three hours. On the third day of this treatment he suffered the first tabetic crises of his career with girdle pain and band-like feeling of constriction around his upper chest. He had no bowel movement for three days and his abdomen was slightly distended. The crises passed and he was discharged at the end of ten days, having recived a total of 8,000,000 units of penicillin.

Five days later he was again observed. He had developed a rolling gait, loss of voluntary bladder and anal sphincter control, a feeling of numbness of both great toes, and the girdle pains and feeling of constriction around his upper chest was constantly present.

Six days later, 21 days after the beginning of penicillin therapy, he re-entered the hospital with a marked increase in all his symptoms and complete inability to walk. The symptoms gradually subsided, sphincter control returned, and at the end of three months the patient was able to get about with the aid of braces and a cane.

It was felt that his symptoms occurring, as is commonly the case, in the first 48-72 hours were due to a Jarisch-Herxheimer reaction brought on by the use of penicillin.

CASE NO. 2

A 49 year old colored male with tabo-paresis and cardiac syphilis (aortic regurgitation) had symptoms of speech and muscular incoordination associated with optic atrophy. He was a cheerful, ambulatory, and privileged patient on the ward for the first twenty-one days of hospitalization. He was started on 10 drops of a saturated solution of potassium iodide on the fourteenth hospital day, and on the nineteenth hospital day he received 1 c.c. of bismuth subsalicylate intramuscularly. On the twenty-first hospital day he was started on penicillin at the rate of 80,000 units every three hours. Two days later he began a rapid mental deterioration, finally necessitating transfer to a mental institution.

Penicillin was not interrupted because we did not at that time think the change to be more than a transitory one. Now there seems to be reason to believe, both from our own experience and from the experience of others,[9] that Herxheimer reactions cause permanent damage. Tucker and Robinson,[9] of Baltimore, report some reactions to the initiation of treatment in 26 per cent of patients. It is impossible to prove that penicillin is the cause of the exacerbation of symptoms as the therapeutic paradox is a well-known fact in central nervous system syphilis.

It would seem wise, however, in cases of general paresis, tabes dorsalis, or progressive optic atrophy, to follow the method of treatment advocated by William A. Leifer.[10] He recommends twenty-four injections of 5,000 units at three hour intervals followed by 180 injections of 50,000 units, making a total dosage of 9,120,000 units.

BAL (BRITISH ANTI-LEWISITE)

During the last war a drug was developed to combat arsenical poisoning from lewisite.[11] It is known that arsenic forms a stable compound with—SH (sulfhydryl) groups in the body tissues preventing them from performing their proper functions. This drug, by virtue of being a dithiol, forms an inert stable compound with the arsenic permitting its removal from the tissues and rapid excretion by the kidneys.

Eagle[12] has made an extensive report of cases in which BAL has been used in complications of arsenical therapy. Sulzberger and Baer summarized his findings as follows:

(a). Arsenical dermatitis: In 88 cases, 80 per cent responded to treatment.

(b). Toxic encephalitis: In 55 patients, 44 recovered completely within one to seven days and 11 died.

(c). Agranulocytosis: In 11 cases, 10 recovered with one death.

(d). Aplastic anemia: In three cases, there was no beneficial effect from BAL.

(e). Jaundice: In 14 patients, five showed prompt response, seven evidenced no effect, and in two the effects were debatable.

(f). Massive overdosage of oxophenarsine hydrochloride: In four cases there were three with prompt improvement and one death.

(g). Arsenical fever: There were 44 cases with prompt recovery in all.

Because gold and arsenic resemble each other clinically and behave similarly in the tissues, BAL was tried in the treatment of gold reactions and proved to be very effec-

tive. In a recent journal of the American Medical Association there was a report of marked improvement in six out of seven cases treated with this drug.[13, 14] Twenty-five out of 26 cases of acute mercury poisoning survived following treatment with BAL.[15]

In treatment of severe gold or arsenical poisoning, it is recommended that 3 mg. per kilogram of body weight of BAL, 10 per cent in oil, be given intramuscularly every four hours for the first few days, five injections on the third day, and two daily thereafter for ten days, or until recovery. In milder cases the dosage may be reduced to 2.5 mgm. per kilogram. In mercury poisoning the initial dosage is usually higher, 5 mgm. per kilogram followed in one or two hours by a dose of 2.5 mgm. per kilogram of body weight. Then as in arsenic poisoning.

Side effects include profound weakness, nausea, vomiting, headache, muscular aches, lacrimation, and salivation.

There follows three cases of arsenic poisoning treated with BAL:

CASE NO. 1

A 36 year old male entered the hospital in an extremely serious condition. He had a generalized exfoliative dermatitis associated with a marked toxemia. He had received seven injections of mapharsen in a period of 27 days for a total of 0.32 gm. The rash started after his fifth injection, was greatly aggravated by the sixth, and became generalized after the seventh. Twenty-seven days after his first symptoms appeared and 12 days after the condition had become generalized, he was given BAL at the rate of 2.5 c.c. of the 10 per cent solution in oil intramuscularly every four hours for a total of 10 injections. The drug was discontinued because of abscess formation at one of the sites of injection in his right buttock and because the patient, ambulatory on admission, had become so profoundly weak from the injections he could not turn over in bed. This side effect of the drug disappeared in the first 24 hours after the drug was discontinued. The response of the patient to the drug began with his first injection. The rash, edema, and toxemia all faded rapidly, and on the twelfth hospital day the patient was discharged with a mild residual dermatitis on his groins.

CASE NO. 2

A 27 year old colored male with early latent asymptomatic syphilis was given 60 mgm. of oxophenarsine hydrochloride and 200 mgm. of bismuth. Three days later he received another 60 mgm. of oxophenarsenine hydrochloride. On the evening of his second injection of arsenic, the patient complained of a severe headache and became stuporous and irrational. A diagnosis of hemorrhagic arsenical encephalitis was made and he was given 2 c.c. of a 10 per cent BAL in oil solution, through error, intravenously rather than intramuscularly. He immediately became cyanotic and dyspneic and appeared to be in shock. The blood pressure was 110/70, pulse rate 60 per minute, the eyes were dilated but reacted slowly to light. There was moderate nucal rigidity present.

The patient was not given any treatment at this time and the next day was given 2 c.c. of BAL intramuscularly. He had improved tremendously over night and except for a slight clouding of his sensorium he was perfectly normal, being discharged on the fourth hospital day as perfectly recovered.

This case should give us some courage in the use of this new drug in that a patient survived an accidental intravenous injection of an oil solution.

CASE NO. 3

That BAL may be of use in chronic arsenical poisoning is best illustrated by the following case. A 45 year old colored female entered the hospital with a chronic generalized exfoliative dermatitis which had become exacerbated in 1937, 1938, and 1942, following her employment in spraying cotton with an arsenical. After three weeks without improvement, she was started on BAL at the rate of 1.5 c.c. of the 10 per cent solution in oil every four hours for two days and then 1.5 c.c. twice a day for five days, then 1 c.c. daily for eight days. On the eighth day she was discharged greatly improved. Her skin was smooth and itching had subsided. Fissuring and thickening of the palms and soles were the chief residue.

CONCLUSIONS

The reactions to penicillin are listed. Special attention has been called to the permanent aspect of the Herxheimer reaction in the treatment of late syphilis.

In BAL we have an extremely safe and valuable drug with which to combat arsenic, gold, and mercury poisoning.

REACTIONS TO BENADRYL AND PYRIBENZAMINE*

The study of any new drug is often speculative, since neither the optimum dosage nor the diseases which should be treated, can be predicted. Furthermore,

*This portion of the paper was presented by Dr. Henington.

side reactions might occur which had not heretofore been mentioned by other observers. Because the new "magic drugs" in general have yielded such disappointing results in most dermatologic problems, it is natural that searches for new specialized forms of management have been pursued with great intensity by the dermatologist. Some advances worthy of mention will be recorded here.

In view of the gradually accumulating evidence that some features of the allergic reaction may be associated with the liberation of histamine, investigation has been directed towards synthesizing compounds that might counteract certain pharmacologic effects of histamine. Several such substances have been studied within the past few years but because of their toxicity have proved unsuitable for clinical use. However, two of these substances have received favorable clinical trial and they have been named benadryl and pyribenzamine, respectively. It appears likely that in the future more compounds in this series will be discovered that may prove to have an even greater pharmacological activity.

Benadryl is a white crystalline powder which may possibly be slightly opalescent. It is soluble in water and alcohol and is stable under ordinary conditions of temperature and pressure. It has been administered orally, intramuscularly and intravenously, and is available in capsules of 25 and 50 mgm. and as an elixir with 10 mg. of benadryl in 4 c.c. (Z/i) of the mixture. The average adult dose is 50 mg., repeated three or four times a day, and the total daily dose has varied from 50 to 500 mg. The elixir in doses of 10 or 20 mgm. (one or two teaspoonfuls), repeated three or four times a day, may be given to children. A child's dose is usually derived by allowing 2 mg. of benadryl per pound body weight divided into two to four doses. The amount of drug required in both children and adults will vary with the severity of the allergic symptoms.

Study at the Mayo Clinic showed that benadryl: (1) decreases the cutaneous vasodilating action of histamine; (2) alleviates the nasal congestion induced by the vasodilatation of the mucous membrane caused by histamine; (3) may decrease the response of the gastric acids and the volume of gastric secretion provoked by the administration of histamine, and (4) depress the wheal and flare response in cases of hypersensitiveness to cold.

Benadryl is readily absorbed by all routes of administration and the maximum response following oral use is about 25 minutes, although it may be as rapid as 10 minutes. The therapeutic action usually lasts for five to eight hours.

No evidence is available to suggest a delayed or cumulative effect. Because drowsiness is encountered in a number of cases, it is well to avoid the concomitant use of sedatives and hypnotics. When the drowsiness is bothersome it may be counteracted in some cases by the simultaneous administration of ephedrine sulfate or benzedrine.

Clinical Use—Urticaria: Contis and Owens[16] prescribed benadryl for eighteen patients with various types of urticarial eruptions, and eleven patients had complete disappearance of the eruption during treatment. Four patients did not respond to the usual dosage of 50 to 100 mgm. given orally one to five times daily.

In treating cases of chronic urticaria, angioneurotic edema and dermographia, when the drug was discontinued there was prompt recurrence of the disease. Of the first 52 cases treated by Todd,[17] 47 were completely relieved, four were partially relieved, and one was relieved of whealing, but not of pruritus.

From these experiences, it appears that benadryl is highly effective in the treatment of angioneurotic edema and urticaria when administered orally in 50 to 100 mgm. doses repeated two to six times a day. In the majority of cases relief is achieved only while the drug is being administered.

Urticaria occurring in serum sickness and following liver injections or penicillin therapy has also been controlled by the use of benadryl. In some instances the relief thus afforded allowed continued injections of the medication.

Hay Fever and Vasomotor Rhinitis: Koelsche, Prickman and Caryer[18] treated 52 patients with hay fever and obtained over 50 per cent improvement in three-fourths of the cases. The dosage employed was 50 to 100 mgm. administered by mouth three times daily. These authors also showed that combining 3/8 gr. of ephedrine sulfate with the benadryl produced an increased amount of relief.

Asthma: Suffice it to say that benadryl has been disappointing in the treatment of asthma. Koelsche, Prickman and Caryer administered benadryl to twelve patients with bronchial asthma and only four reported relief. Of three cases reported by the Mayo Clinic, one was improved.

Benadryl has been prescribed in a variety of other unrelated conditions to achieve an antihistamine or an antispasmodic effect. Among these disorders are contact dermatitis, migraine, Ménière's syndrome, erytherma multiforme and dysmenorrhea. Whether it will prove effective in these and in other conditions is not clear, and its effectiveness will undoubtedly be the subject of future studies.

Reactions: No skin eruptions or febrile disturbances have been reported following its use and it is not habit forming.

Clinical observations on the use of benadryl: All "serious reactions" to benadryl thus far reported have occurred in patients practicing self medication, who have substantially increased the dose prescribed by the physician. Borman reports the case of a Catholic nun who took 40 capsules of 50 mg. each in a period of 24 hours (2,000 mg.). She became disoriented, lethargic and confused. The drug was immediately discontinued when she consulted a physician, and she recovered completely in twenty-four hours. Geiger and his group[19] in the A. M. A. report a case of complete shock following a normal amount of benadryl, namely, 50 mg., three times a day. After the first day of treatment, the patient complained of palpitation, dimmed vision, malaise without drowsiness and heartburn with nausea. Following the next regularly scheduled dose of benadryl (making a total of 350 mg.), the patient was found unconscious in bed, cold, pale and pulseless. The blood pressure could not be obtained. A solution of epinephrine 7½ min of a 1:1,000 was given subcutaneously, and all medication stopped. Within 30 minutes the pulse was palpable, though weak. In three hours the patient was completely normal, with no recollection of what had happened. Although up to this time no deaths have been reported from benadryl, it is reasonable to assume that a patient taking the drug and not having the advice of a physician might well take an over dose and continue it until death is produced.

PYRIBENZAMINE

Pyribenzamine is a synthetic compound which manifests a pronounced capacity to prevent many of the pharmacologic actions of histamine. Pyribenzamine on a weight basis is approximately six to seven times more active than benadryl in preventing fatal histamine shock in guinea pigs. Other experimental work on animals indicates that its activities are similar to benadryl and that it has relatively low toxicity. Studies in animals and man receiving pyribenzamine over notable periods of time have failed to reveal any untoward effects or the development of any significant tolerance to the drug. The exact mode of action is unknown. The average adult oral dose of pyribenzamine is 50 mg., repeated four times daily, preferably after meals. The total in adults has varied from 50 to 600 mg. depending on the severity of the allergic symptoms. In children a dose of 10 to 25 mg. repeated three or four times daily may be effective. The drug is available in tablets of 25 to 50 mgm. and suppositories 50 and 100 mg. respectively.

There is a marked similarity between pyribenzamine and benadryl, therefore, their uses parallel one another. Arhesmon and Koepf[23] studied 277 patients treated with pyribenzamine and they noted that relief of symptoms occurred within 15 minutes and persisted for four to six hours after the ingestion of the drug. In some instances a total daily dose of as much as

1000 mg. was given without untoward effect.

The experience with hay fever and urticaria treated with pyribenzamine was very similar to the benadryl studies. Thus, of 140 patients afflicted with grass and ragweed hay fever, 85 per cent had relief of symptoms. Of 15 patients with acute urticaria, all but one were notably relieved of symptoms. There were 44 patients with chronic urticaria and of these, 63 per cent were improved after taking pyribenzamine. The results of treatment of bronchial asthma were not satisfactory, but 46 per cent noted definite relief of bronchial symptoms when ephedrine sulfate and pyribenzamine were administered together a more notable improvement was obtained.

Side-Reactions: Side reactions are common, but rarely serious and in many cases do not demand that pyribenzamine be discontinued. The larger the dose employed, the more frequent will be the side effects. Drowsiness, dizziness, faintness, nausea and vomiting are the more common undesired effects. In some instances nervousness, drying of the mouth, and palpitation may be experienced.

The "serious reactions" occasionally seen with the administration of benadryl have thus far not been seen with pyribenzamine, making it, therefore, a relative harmless drug, yet having many beneficial effects. It is worthy to note that occasionally a patient can take both pyribenzamine or benadryl the first time without any reaction, but if it becomes necessary a week or a month later for the patient to take the drug again he will become drowsy and have many of the side reactions that we have just mentioned. Occasionally the reactions will be so uncomfortable that the drug will have to be discontinued.

FURACIN

Furacin is a lemon-yellow crystalline compound, slightly soluble in water, in alcohol, propylene glycol, and is most soluble in carbowax; therefore, the ointment is manufactured in a carbowax base. Furacin is produced by synthesizing pentose sugar from oat hulls and bran; these are chemically dehydrated to furferal and to this is added the nitro and semicarbozone groups to form furacin.

For the present, furacin is offered only in the form of furacin soluble dressing, a preparation for topical application in the treatment of infected wounds and surface infections, and for the prevention of wound infection. It contains 0.2 per cent furacin in solution. The pH is between 5 and 7.

Furacin soluble dressing becomes almost liquid at body temperature. It dissolves in serous fluids, blood and pus, thus reaching all parts of wounds. It does not cake or otherwise interfere with wound drainage. Furacin soluble dressing is a 1-500 solution of furacin in a water soluble vehicle containing carbowax 1500 and propylene glycol.

Indications: Based on the clinical findings to date, furacin soluble dressing is suggested for local application in the following conditions:

1. Infected surface wounds, or for the prevention of infection.
2. Infections of third and fourth degree burns.
3. Carbuncles and abscesses after surgical intervention, where conditions permit this therapeutic agent to reach the entire infected area.
4. Infected varicose ulcers.
5. Superficial ulcers of diabetics.
6. Secondary infections of eczema.
7. Impetigo of infants and adults.
8. Treatment of graft sites preparatory to skin grafting, and later to prevent infection.
9. Osteomyelitis associated with compound fractures.
10. Secondary infections of dermatophytoses.
11. The work of John Downing and his associates have also found furacin soluble dressing to be of beneficial effect in the treatment of many dermatoses, namely: infectious eczematoid dermatitis, erythema, sycosis vulgaris, dermatitis venenata with secondary infection, acne vulgaris, and diabetic and hypostatic ulcers.

Furacin's antibacterial spectrum includes both gram-positive and gram-negative organisms.

Methods of Applying Furacin Soluble Dressing: Surgeons now using furacin soluble dressing are applying it in various ways. It may be spread on gauze which is then laid over the wound and held in place by bandages, or applied directly to the affected area without bandaging. Moderate amounts may be placed in deep wounds and cavities and covered with a dry dressing. Furacin soluble dressing may be melted and poured over the wound. Some physicians advocate changing dressings one to three times every 24 hours. I usually suggest more frequent changing of dressings in weeping lesions, whereas in dry, inflammatory dermatoses one change every 12 hours is usually all that is required. For examination of wounds, the dressing may be rapidly and completely removed by irrigation with water or saline.

Drainage of pus pockets, removal of foreign and necrotic material and sequestra should always precede application of the dressing.

For skin grafts, furacin soluble dressing is applied both to the denuded area to combat infection and facilitate granulations and to the donor area to prevent infection.

Reactions to Furacin Soluble Dressing: Both the low toxicity of furacin and its low concentration (0.2 per cent) in furacin soluble dressing make highly improbable the possibility of producing systemic toxic effects from local application. Sensitization phenomena both locally at the site of the application of furacin and areas removed from the local site have been reported[24] and have been seen occasionally by us. Most reactions have occurred in patients who have been treated with furacin over a long period of time, that is a month or more. Previously eczematized areas are more likely to react to the drug than are new and clean wounds. The reactions thus far have not been serious although occasionally they have been of a generalized eczematoid type and have lasted for a week or two. Sensitization is thought to be due either to the carbowax or the propylene glycol and not the furacin *per se*: work is being done now by the manufacturer to eliminate the sensitization properties of furacin soluble dressing.

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THE CHEMOTHERAPY OF LEPROSY*

HERMAN GRAY, M. D.

NEW ORLEANS

INTRODUCTION

This paper was written with the intent of reviewing some of the attempts made to find a drug or drugs useful in the cure of leprosy. The material first suggested itself as suitable for a thesis subject and I first became interested in it after having talked with Dr. R. M. Wilson at Christmas, 1945, just before his return to Korea to take charge of the leprosy work in the United States Zone of that country. In the spring of 1946, my interest was firmly aroused upon hearing of the sulfone drugs then being used at the National Leprosarium in Carville, Louisiana.

The following material was gathered from reports in the literature and conversations with a number of leprologists—Drs. Wilson, McCoy, Faget, Johansen, Fite, Wolcott and Kellersberger; also, the photographs and exhibits in the laboratory at the Carville Leprosarium, demonstrated by Sister Hilary Ross, served to emphasize the treatment results.

In the discussion of the subject, I have taken the liberty to precede the actual drug therapy of leprosy with some more general remarks on the disease and its general treatment. Also, I have introduced the discussion of the individual drugs tried in the fight against leprosy with some statements of Muir on the evaluation of such drugs. Some of the substances represented in the literature by only one article have been excluded. Several physical agents which have been used from time to time in the treatment of leprosy, such as ultraviolet irradiation, x-ray irradiation, and the use of the Kettering hypertherm, have likewise been excluded. Incidentally, they have not been found of antileprotic value. Surgical excision of early lesions is also not discussed, though it has been successful in several instances.

GENERAL INFORMATION

History, Geographic Distribution and Prevalence: Leprosy has been talked about and described in writing since antiquity. Herodotus, the Cappadocian, in the Second Century, A. D., gave the first clear-cut picture of the disease. Since then such descriptions have not been lacking. The leper was dreaded in ancient times for his loathsome appearance (if he were in the advanced stages of the disease), and the fear of the supposedly extreme contagiousness of leprosy made its sufferer an outcast from men's society. This attitude toward the leper still prevails in large measure, and therefore, the sociologic aspects of the disease are of great importance.

Leprosy has been endemic in China, India, and the Nile Valley for many hundreds of years before the birth of Christ. In 480 B. C., the Persians brought it to Greece, and in 62 B. C., the Romans introduced leprosy in Europe. Segregation of lepers was practiced as early as 1500 B. C. by the Babylonians. During the sixth and seventh centuries the disease appeared in northern Europe, and it spread widely in the time of the Crusades. In the Middle Ages it slowly decreased in frequency in Europe and is now rare. In India, China, Japan, the East Indies, Philippines, Middle East, and Africa, it is still common.

How and when leprosy reached the New World—whether by white European settlers or from the negro slaves brought over from Africa, is not clear. There are now some 30,000 lepers in the Western Hemisphere.

In the United States, 385 lepers are now being treated at the National Leprosarium in Carville, Louisiana. Some 1,000 to 2,000 others probably dwell in the United States, many of them hiding the disease; others still undiagnosed. Most of the lepers in the United States come from Louisiana, Texas, Florida, and to a lesser degree, California.

It is estimated that there are three million lepers in the world today. Of these, according to Muir, one million live in India,

*Awarded the Walter Reed Memorial Medal for the best thesis on a subject having to do with tropical or preventive medicine presented to Tulane Medical School.

another million in China, a half million in Africa. About 10 per cent of all lepers are under some sort of medical surveillance.

Etiology: A. Armauer Hansen, working in Bergen, Norway, in 1874, first saw an acid-fast bacillus which was very numerous in leprous tissues and he considered it the etiologic agent of the disease. The bacillus has since been named *Mycobacterium leprae*. Though known for over 70 years, this bacillus has never been satisfactorily cultured. That is, no one has been able to reproduce the results of those who claim to have cultured it, nor have animal inoculations been successful. In experimental work, therefore, it has been necessary to use rat leprosy, with the assumption that the bacillus of rat leprosy, *M. leprae murium*, has similar characteristics to *M. leprae*. Tuberculosis has also been used in the comparative analysis of various antileprotic drugs.

Epidemiology: Because the incidence is twice as great in men as in women, it has been thought that women are more immune to leprosy than men. Hopkins believed that negroes in Louisiana were more immune than white people.

The disease usually begins in childhood, adolescence, or early adult life. Rogers emphasized and showed statistically that 80 per cent of lepers come from homes in which a leprous person has resided for a long period of life. He reiterated the view that leprosy is a disease transmitted through long, intimate association with a leper, especially during the childhood years. The average age of admission, in one large series, to a leper hospital was 16 to 20 years.

All leprologists agree that the disease is only feebly contagious. The public's fear of leprosy is unfounded, for a casual contact with a leper is hardly conducive to infection. Rather, it is the long, intimate home association that spreads the disease.

In the United States, only the states bordering the Gulf of Mexico have repeatedly new cases of leprosy. In Minnesota, for instance, 200 Norwegian lepers settled in the latter half of the Nineteenth Century, yet the disease died out. On the other hand, new cases continue to crop out in Louisiana, Texas and Florida. Perhaps the difference in climate is a determining factor in this problem.

Symptomatology: After an incubation period of one to 10 years or more, the disease begins to manifest itself. Rogers showed that in four-fifths of patients, the incubation period was less than five years.

Leprosy is classically divided into two types: nodular (lepromatous) and nerve (maculo-anaesthetic) leprosy. In cooler climates, two-thirds of the cases are nodular, while in tropical regions about two-thirds are of the nerve type.

Nodular leprosy begins with an outbreak of brownish-red macules which thicken and become pigmented. There is often associated irregular fever. The most common sites of eruption are the ear lobes, nasal alae, forehead, eyebrows, cheeks and skin. The eyebrows fall out. The nodules come and go and slowly spread and thicken. The skin of the entire face becomes greatly thickened, first hyper-, later anesthetic. The spots do not sweat. Folds are formed, and the thickened, wrinkled face is aptly described as "leonine." Eye involvement (conjunctivitis and iridocyclitis) is frequent, and blindness often results. Ulceration of the lesions is frequent. The patient finally, after several years, becomes cachectic, and somnolence precedes death.

Nerve leprosy results from the irritation of the granulomatous tissue surrounding peripheral nerves (especially the ulnar, anterior tibial, peroneal and facial nerves) with resulting neuralgia and paresthesia, finally anesthesia of the tissue supplied by the nerve. Anesthetic spots on the covered portions of the skin are pale, have an erythematous border. The skin becomes atrophic in these areas. Nerve trunks enlarge, especially the ulnar. First they are tender, later painless. Because peripheral anesthesia occurs, trophic changes and traumatic lesions of the toes and fingers give rise to absorption of the phalanges and large, non-healing ulcers on the exposed portions of the hands and feet. Contractures of the fingers and muscular palsies and

atrophies also result from the nerve atrophy.

The mixed type, seen frequently, is a combination of the nodular and nerve type.

Pathology: Granulomata containing swollen, bacilli-filled, pale-staining cells (globi) are found. These occur in the skin and subcutaneous tissue. In acute "lepra fever" episodes the bacilli may be recovered from the blood. In nerve leprosy the peripheral nerves are swollen. Cellular proliferations in the region of the blood vessels, later in the perineurium and finally the endoneurium compress the axis-cylinder with consequent degeneration.

Diagnosis: Aside from the identification of the signs and symptoms of leprosy, the most important procedure used in the diagnosis of leprosy is the recovery of the bacilli from a skin or mucous membrane (for example, nasal) smear or biopsy.

Prognosis: On the whole, the prognosis is unfavorable. Although spontaneous improvements occur at intervals, relapses usually follow. The nodular type runs a more progressive course than the nerve type. Patients with nerve leprosy may live 20 to 40 years. Tuberculosis and nephritis are the two complications which may carry the leper off within a few years of the onset of his illness.

Prophylaxis: Since the beginning of recorded medical history, segregation has been the chief tool in the leprosy control program. In past centuries, this segregation was so intense that the leper could not associate with any non-leprous person. He was treated worse than a criminal and deprived of all civic rights. In the Middle Ages, special hospitals in Europe were built to care for the lepers, and since that time segregation in special institutions has been the most common usage.

Rogers pointed out that compulsory segregation had failed wherever it had been tried, for the lepers were afraid of being "incarcerated" in a hospital and therefore hid themselves. The result of this concealment of the disease was a further spread and often advancement of the leprosy in these people to a hopeless degree, before they were finally found and brought in for treatment. Rogers believed that for the vast majority of the world's lepers the most feasible, efficient, and economical method is a voluntary system to supply the most up-to-date treatment for early cases at clinics, and for more advanced ones in leper colonies with land to cultivate to supply most of their food and afford exercise for the patients.

Rogers[1] has stated: "For the rapid reduction of leprosy incidence, it is essential to adopt my plan of examining the households and other close contacts of all known infective lepers at not less than 6-monthly intervals for at least 5 years, with early treatment of the early cases thus detected." This plan proved successful on Nauru Island over a period of three years, with a reduction of the leprosy prevalence by 40 per cent.

It is essential to separate newborn children born of leprous parents from their parents immediately after birth. Special "healthy children" institutions have been evolved to take care of such children.

General Treatment: Patients must not only receive therapy with the drug in vogue, but they must also have supportive treatment. This supportive treatment is of great import in leprosy, since the disease is so long-lasting. Also, it is imperative to diagnose and eliminate any other diseases from which the patient happens to be suffering.

Non-specific treatment of local manifestations of leprosy must also be considered: Ulcers, especially on the legs and feet, have been treated with urea crystals applied locally daily, to hasten the extrusion of necrotic tissue and bone. In the Carville Leprosarium, streptomycin filtrate wet applications have been found to be effective. Nerve pains can be controlled with novocaine stellate ganglion or lumbar sympathetic block. Muir[2] advocates ephedrine given orally in capsules ¾ to 2 gr.

Lepra reactions have been variously handled: Large doses of alkalis (sodium bicarbonate) have been tried to counteract the acidosis. Empirically, fuadin, 5 gm.

given intramuscularly, will often stop the severe fever in one to two days.

A diet well-stocked with proteins, carbohydrates, fats, and vitamins is necessary to make up for the weight loss and malnutrition so commonly seen in the lepers, especially in tropical countries. Also optimum nutritional state of the body helps to combat the wasting process resulting from the disease itself. Fresh meat, vegetables, fruit, and dairy products play a large role in the dietary regime. Dr. Basler, who has been in charge of a large leper colony in Nigeria for 10 years, told in a personal conversation how this dietary improvement alone produced a remarkable remission of the disease in many patients he has had under his care.

Lepers are often very despondent for they come to feel keenly their separation from even their dearest family members forced upon them by the rest of society. They may thus feel useless, even become sullen. Therefore, it is of importance to give them something to do while they live for prolonged periods of time with their fellow-lepers under institutional care. Vocational therapy, recreation facilities, religious services—all these play a large part in the treatment of leprosy. In regard to vocational therapy, the work often consists of dairy or truck farming, small "craft shop" goods manufacture, housework (cooking, sewing, and so on) for women. Recreational facilities can be developed with a band or orchestra, theatrical performances, glee club, games of both physical exertion and mental concentration varieties. Self-government of the patients has proved very popular at Carville, Louisiana. School for children and lectures for adults, are other things to be considered in this program. Provision of religious instruction and worship also must not be forgotten.

When the disease becomes "arrested,"—lesions becoming stationary and disappearing, and general health becoming robust—the patients are usually discharged from institutional care but are biannually examined for any recurrences.

SPECIFIC ANTILEPROTIC DRUGS

The Evaluation of Antileprotic Drugs: When reading about various drugs and their effects on leprosy, one is impressed by the glaring discrepancies of results obtained by different investigators using the same methods. Several important points, according to Muir, should be stressed in the judgment of the efficacy of drugs. The application of evaluation to chaulmoogra oil and its derivatives can be used as an example of the evaluation of the other drugs.

The first factor is the difficulty of classification of leprosy. The nodular type has the worst prognosis, the tuberculoid variety of nerve leprosy (of the Cairo classification) the best, with frequent spontaneous recoveries. Thus, spectacular cures of "nodular leprosy" may really have been tuberculoid patients who spontaneously recovered.

In the second place, there is a distinct difference between the incidence of the more severe nodular leprosy and the milder nerve leprosy in the tropics and in temperate climates. Most people have a high resistance to leprosy; only a small minority is easily infected. In temperate regions where leprosy is endemic and people live "hygienic" lives, only those with a low resistance will be sufficiently exposed to the disease to contract it. However, in the tropics, where people live crowded together, eat poor diets, live under conditions of filth and squalor, a much greater percentage of the population is exposed to leprosy than in temperate regions. Therefore, the milder nerve leprosy is more common proportionately, although the total number of cases is great. Because, then, the few cases treated in temperate regions are "nodular," therapy results are poorer than in the tropics, where most of the patients treated have the milder "nerve" type of leprosy.

No one has yet carried out a proper test for the efficacy of chaulmoogra oil in leprosy. For such a test, Muir stresses the use of the Lepromine test, which should be negative (indicating lack of resistance to leprosy) for six months before treatment, plus clinical and bacteriologic evidence of

activity. Secondary infections must be ruled out. Control cases should be treated with a bland injection of a similar substance,—olive oil, in the case of chaulmoogra treatment. Such a program must be carried on at least two years, a difficult project at best.

McCoy,[3] in summing up his views on the value of chaulmoogra, wrote in 1942: "My own observations have led me to the conclusion that the oil and its derivatives are of little or no curative value, and that the unpleasant side effects probably outweigh any advantage to the patient that may accrue from their use." Dr. McCoy, in a personal conversation, recently stated that he could find no use for the chaulmoogra derivatives in leprosy treatments.

The requirements for an ideal antileprotic drug, according to Muir, are: (1) It must be of sufficiently low toxicity so that, at least after the early stages of treatment, it can be safely administered without requiring elaborate tests, requiring considerable skill and time, and can be tolerated over a sufficiently long period of time; (2) it should be easy to administer and capable of being given by mouth; (3) it must be able to bring about steady improvement in the average case until the disease entirely disappears, and to prevent relapse; (4) it should be easy to manufacture and therefore capable of being produced at low cost in large quantities.

Chaulmoogra Oil and its Derivatives: *Source and Properties*: Chaulmoogra oil is obtained from the seeds of several trees found in the family *Flacourtaceae*, in particular from *Taraktogenus kurzii*, a tree found in Assam and Burma, *Hydnocarpus wightiana*, which grows in southern India and *H. anthelmintica* in Malaya and Indo-China. The oil of *Gynocardia odorata* does not contain the same fatty acids. The oil contains two unsaturated fatty acids with a closed ring consisting of five carbon atoms, a structure peculiar to this series of oils. The *Hydnocarpus* trees have been grown in Africa and South America to provide chaulmoogra oil for the local treatment of lepers.

In ancient China and India, chaulmoogra oil was used in the treatment of leprosy. In the Chinese medical book, *Pen Tsao Kang Mu*, written about the fourteenth century, the following prescription is given: "Take 3 catties of the seeds, remove the hulls and grind to a fine powder. Discard those that have turned yellow. Pack in an earthen jar and seal tightly. Put the jar into a pot of boiling water and seal the pot so that no steam escapes. Boil until oil assumes a black and tarry appearance. It is administered in the following way:

Sophora flavesceus	3 ounces
Chaulmoogra oil	1 ounce

Mix into a paste with wine and make into pills the size of the stersulia seed. Take 50 pills with hot wine before meals."[4]

A good description of the current native practices in prescribing chaulmoogra oil at the time and the properties of this substance is given in Watt's *Dictionary of the Economic Products of India*, 1890: "Chaulmoogra oil has long been known and used in the East as a cure for leprosy. In native practice of the present day the seeds and oil (of *Taraktogenus kurzii*) and of the closely-allied *Hydnocarpus wightiana* are both largely employed and are as a rule administered with "ghi" (clarified butter). As sold in the bazaars, the oil is commonly impure. The expressed oil is clear and of a pale sherry color and possesses a characteristic colour and odour. On being kept for some time it throws down a granular fatty deposit. Of late years the knowledge and use of the drug have spread to Europe, where it appears to be increasing in favour and reputation. The reputations of the drug most in repute in Europe are the pure oil and gynocardic acid, which is supposed to be the active constituent.

"Oil of *H. wightiana* is of a sherry yellow colour and devoid of the characteristic taste and odour of that of *T. kurzii*. Unlike the latter, which it otherwise closely resembles, it does not at ordinary temperatures deposit a crystalline fatty acid. It is chiefly employed as a lamp oil in Goa. The medicinal properties of this oil were neglected by Europeans until recently when they began to substitute it for the more expensive oil of *T. kurzii*. The oil must be used with a

certain degree of caution, as in certain cases it acts as a gastrointestinal irritant and produces vomiting and purging."[5]

Monat, the first European physician to use chaulmoogra oil, in 1854 administered it in the form of the powdered seeds. Dr. Paul, Professor of Surgery at Madras Medical College, wrote in 1857: "In 1855 the therapeutic virtues of the Hydnocotyle and Choul Moogre received a fair trial at the hands of Dr. Porteous, and they were found to produce no amelioration."[6] Dr. Bhan Daji reported several cures of leprosy with chaulmoogra oil in 1870. He charged such exorbitant prices that when the people who flocked to him found out he was but reviving the use of chaulmoogra oil, long known in India, his fame was short-lived.[7]

Mode of Action: The mode of action of chaulmoogra oil in the therapy of leprosy has been speculated upon by numerous investigators. In 1903, Talwik wrote that the oral administration of the drug produced leukocytosis, and the leukocytes destroyed the leprosy bacilli. Williams and Forsyth,[8] in 1909, concluded that "substances containing unsaturated fatty acids (e. g. cod liver oil, chaulmoogra oil) have the power of disintegrating the waxy envelope which surrounds the tubercle bacilli." Mercado, in 1915, was of the opinion that the therapeutic effect was due to the phagocytic action induced by the leukocytosis. In 1920 Rogers reiterated the views of Williams and Forsythe. Because he thought any unsaturated fatty acids would have the same bacteria capsule-dissolving properties as chaulmoogra oil, he therefore used the less irritating cod liver oil (sodium morrhuate) and Soya bean oil.

In the same year McDonald and Dean at the University of Hawaii and Walker and Sweeney concluded from the "bactericidal action" of the chaulmoogra oil on rat leprosy bacilli and other acid-fast organisms, an action not seen in other fatty acids, that the chaulmoogra series fatty acids were active against those bacilli on account of their unique molecular structure,—a 5-cyclic carbon ring. Walker and Sweeney considered three possibilities as to the mode of action of the oil: (1) It could have a direct bactericidal effect on *M. leprae;* (2) it could act indirectly by stimulating the tissues to react against the bacillus; (3) it may be inactive and improvement occur spontaneously. "An hypothesis which seems best to explain the mechanism of the bactericidal action of the chaulmoogra acids and their specificity for acid-fast bacilli is that these fat-elaborating bacilli attempt to utilize the chaulmoogra acids to build up their fatty capsules, and that these cyclic fatty acids contain a group or an arrangement of atoms which is toxic for the bacterial cell."[9] Schobl, in 1923, also considered the action of chaulmoograte to be due to their specific X-carbon cycle structure. Leukocytosis brings about the contact of the drug with the bacilli, according to Read, 1925.

In 1931 Muir wrote: "An important point for consideration is the manner in which hydnocarpus oil and its preparations act when injected into the tissues of the body. When injected into lesions by the intradermal method, there seems to be little doubt that a large part of the action is due to the local irritation set up, and that this irritative effect continues for a considerable time, the esters remaining unabsorbed inside the local cells. This results in breaking down and phagocytosis of the lepromatous material. Again, there is reason to suppose that the material set free locally may have an antigenic effect and result in the formation of antibodies which have a beneficial effect both locally and in other parts of the body. Both the injections given into the lesions and those given intramuscularly at a distance from the lesions probably act to a large extent by producing an effect analogous to protein shock; and it has been shown that protein shock produced by other methods, such as intravenous injection of dead bacteria, is distinctly beneficial in clearing up leprous lesions."[10, 11]

Lara and Lagrosa injected a small series of patients with the ethyl esters of chaulmoogra oil intramuscularly and in addition gave intradermal chaulmoograte injections on one side of the body and intradermal in-

jections of other vegetable oils on the other. They concluded that the chaulmoogra esters cleared up lesions on "their" side of the patient's body, while the other oils did not. However, they admitted that the series (14 patients) was too small to be definitely significant.

In the 1930's a group of pharmacologists at the University of California led by Emerson, Anderson, and Leake investigated the action of numerous drugs used against leprosy on rat leprosy, other acid-fast bacilli and on leprosy patients. From their extensive studies they concluded that the chaulmoogrates had a specific though not very pronounced effect on the disease, mediated through the unsaturation of the fatty acids, their optical activity, and their basic structure, the pentacycle group. Three agents survived this investigaton: ethyl chaulmoograte, chaulphosphate, and a non-chaulmoograte, merthiolate. The ethyl chaulmoograte had a lower toxicity and was less irritating in animals than the other derivatives. Its therapeutic index was found to be higher than that of the other oil-soluble fatty acid derivatives. Its disadvantage consisted in its very slow systemic absorption, though it cleared local lesions. Because of this disadvantage of the ester, these authors developed a water-soluble derivative, to be administered intravenously,—di-chaulmoogryl-betaglycero-phosphate, called chaulphosphate for short. It did not show the untoward side effects seen in other water soluble intravenously administered derivatives, namely hemolysis and venous sclerosis.

As previously mentioned, McCoy[3] considers the chaulmogra drugs to have little or no therapeutic effect in leprosy.

It is now in order to consider the various chaulmoogra preparations, their manner of administration, advantages, disadvantages, and effects.

Chaulmoogra Oil: The oil itself, as found in the unprocessed seeds, was used in India and China in ancient times. It was found that if the seeds themselves were eaten, little or no nausea resulted, while the oral administration of the expressed oil was fraught with gastrointestinal tract complications. Hopkins, in 1916, reported on the oral adminstration of chaulmoogra oil. He recorded 48 per cent of his patients as "improved," 17 per cent as "cured."

Cochrane[12, 13] sums up well the oral therapy: "Prior to the advances in purifying the oil, it was only possible to give it by mouth. If a patient is able to tolerate large doses by the mouth the disease will undoubtedly improve. Unfortunately, one cannot give, as a rule, large enough quantities to produce permanent results. The method of administration is to commence with 1 or 2 mm. in milk or other suitable vehicle, or the drug can be placed in gelatin capsules and given directly after meals. The dose is first given once a day, then increased to three times a day. Every other day the dose is increased by 2 mm. until about 100 mm. three times a day is reached. Seldom, however, can such large doses be tolerated, firstly because of the vomiting that the drug produces, and secondly because in large doses there is a tendency for toxic symptoms to appear, such as languor and emaciation. If the dose is persisted in when signs of intolerance have appeared there are dangers of fatty degeneration setting in."

Crude chaulmoogra oil has also been given by hypodermic injection. Tortoulis Bey, in Egypt, had a patient in 1894 who had severe vomiting after the oral therapy, and therefore had only been treated sporadically for a period of three years. Bey, therefore, injected the drug subcutaneously for a prolonged period of time, four years. The man's advanced lesions slowly healed. The disadvantages of injections of the crude oil are that there is marked local irritation, and the great viscosity of the oil makes it hard to inject.

Heiser-Mercado Mixture: In the Philippines, 1910, Seiser and Mercado brought out their "mixture", designed to be less irritating when injected subcutaneously than the crude chaulmoogra oil. The mixture was made up of 60 c.c. of camphorated chaulmoogra and olive oil with 4 gm. of resorcin. Even with this mixture, pain after intramuscular injection was common.

Gynocardic Acid and Gynocardates: Moss, in 1879, isolated a crystalline fatty acid with a melting point of 30° C. from commercial chaulmoogra oil. This substance he called "gynocardic acid", because he mistakenly thought chaulmoogra oil was obtained from *Gynocardia odorata*. Cottle reported on its oral use; Roux, in Paris, used it in 1891. In the same year Merck and Company prepared commercial gynocardic acid. In 1904 Power produced the salts, sodium gynocardate and sodium chaulmoograte.

It remained for Sir Leonard Rogers to popularize the chaulmoograte salts. He used a 3 per cent solution of sodium hydnocarpate. It was so irritating when injected subcutaneously or intramuscularly that it had to be administered intravenously. The disadvantages in this manner of injection were resulting thrombosis and phlebitis of the veins, a frequent occurrence. Also, there were occasionally severe fever reactions. The advantage, on the other hand, was easy injection, for the salt had a low viscosity and flowed well through the needle. Rogers then changed his injections to the sodium salt of the low melting point fatty acids found in chaulmoogra oil. This, in 3 per cent solution, he called "alepol." This material was given twice weekly, beginning with 0.5 c.c. and increased by 0.5 c.c. weekly up to 5.0 c.c. or more. Alepol has been used extensively in India by Rogers and his fellow workers and students. Certain economic advantages of alepol over other chaulmoogra products exist: It is packed as a powder for shipping and is therefore cheap to transport. The drug itself is cheap. Also, 1 per cent novocaine can be added to make injections painless.

Ethyl Esters of Chaulmoogrates: The ethyl esters of the acids in chaulmoogra oil have been the most widely used chaulmoogric substances in the last two decades, and they were recommended as the "most efficacious" agents in the treatment of leprosy at the Cairo Leprosy Conference in 1938. However, the Congress emphasized that chaulmoogra treatment should be suspended during a lepra reaction. One advantage the esters have over the plain chaulmoogra oil is that they are liquid at all ordinary temperatures, while the oil itself must be heated before injection to overcome its great viscosity.

The esters were first produced in 1904 by Power. However, it was Engel Bey,[14] in Cairo, who wrote to Bayer and Company of Elberfield, Germany, in 1909, with the request "to see whether they could not obtain a pure preparation of the active principle of the oil or at least a purified article free from the injurious effects of the ordinary oil." The Bayer Company chemists produced the ethyl esters of the total fatty acids found in chaulmoogra oil and called the product "Antileprol." This substance was injected intramuscularly and found to be much less irritating than the purified chaulmoogra oil. Bey initially also gave it orally to some of his patients and noted that gastritis did not occur. The oral dose used was 2 to 5 gm. per day, beginning with 0.5 gm. Since then, it and the other ethyl esters have only been given parenterally.

In 1917, McDonald and Dean[15, 16] and Hollman,[17] in Hawaii, began their work on the ethyl esters of fractions of the fatty acids of the chaulmoogra series. In 1920, they reported the successful use of mixed ethyl esters of the total fatty acids of chaulmoogra oil, adminstered intramuscularly, with the addition of 2 per cent iodine to decrease the irritative qualities of the chaulmoogra. The drug was given in the gluteal muscles once or twice a week, beginning with 1 c.c. doses, later increased to 5 or 6 c.c. After two years of treatment, they discharged 48 out of 186 treated patients as "arrested." In a report in 1922, Hollman tabulated 84 discharged patients and wrote that 60 were tuberculoid and 24 anesthetic. If this classification is the same as that now used, then one could expect to have a number of spontaneous recoveries from true tuberculoid leprosy, and the anesthetic type is also less severe than the nodular variety of which Hollman says nothing. On the other hand, if tuberculoid in his report

means true nodular leprosy, then these arrests of the disease are of significance.

Moogrol, a commercial preparation of very similar nature and sold by Burroughs Wellcome and Company, has also been widely used.

The most numerous articles on the use of chaulmoogra ethyl esters have come from the large Culion Leper Colony in the Philippines. There, four to five thousand patients have been constantly under treatment, and thus these reports have usually dealt with fairly large numbers of patients. At Culion, the Dean ethyl esters were primarily used in the 1920'c and 1930's, with the addition of 0.5 per cent iodine, this mixture having been found to be the least irritating. Lara, however, thinks iodine has some other manner of producing its beneficial action. Not only were the esters given intramuscularly (and subcutaneously near lesions), but intradermally at the site of leprosy lesions. This intradermal injection technic was also called the "plancha" or infiltration method: 0.5 to 5.0 c.c. of the esters are injected, given in small amounts over the areas of the lesions, 5 to 10 mm. apart. The areas may not be reinjected until one month later, or sloughing will result, since it has been shown that the fat globules will remain in the local cells for several months.

Treatment with chaulmoogra oil, as in any other drug, must, of course, be continued for at least one year, and preferably longer, before any results can be ascertained. After reading a large number of articles on the chaulmoogra treatment, one becomes impressed with the claims of slow regression of lesions, shrinking of swollen, painful nerve trunks after local chaulmoogra ethyl ester injections, and reports of discharges of a fair percentage of patients. Yet, the statistics are so inconstant among different observers and in different regions of the world, and also the evaluation of results is made so difficult by the varying classifications of the types of the disease, that one hesitates to quote such statistics. Perhaps it is best merely to reiterate the statement of the 1938 Leprosy Congress: "Chaulmoogra oil from Hydnocarpus species and its ethyl esters administered intramuscularly, subcutaneously and intradermally remains the most efficacious agent for the special treatment of leprosy.[18] (Of course, the newer drugs, sulfones and streptomycin, have appeared since then).

Toxicity: The toxic effects of chaulmoogra oil and its derivatives may be divided into several groups: (1) Immediate effects occur. These consist of coughing, choking and a sensation of dizziness. Although distressing, these symptoms are not important. (2) Next, there are local effects at the site of injection. They consist of inflammation of the tissues and even abscess formation. (3) There are also general symptoms, such as headache, malaise, and fever. (4) Respiratory tract symptoms, with chest pain and oppression and cough. These symptoms are the most important ones, for tuberculosis is the most common complicating disease of leprosy. Thus, pulmonary irritation must be avoided. Likewise, chaulmoogra treatment is contraindicated when a leprosy patient also has tuberculosis. (5) Another reaction which occurs following chaulmoogra reaction is the mysterious "lepra reaction",—a severe febrile attack preceding or accompanying new skin lesions. (6) Kidney disturbances have rarely been observed, but nephritis, another complication of leprosy, is a cause for caution in the pursuit of a course of chaulmoogra. Wade found the ethyl esters of chaulmoogra with 0.5 per cent of iodine added to give the least number of reactions of any of the varieties of chaulmoogra compounds.

Histologic Changes: After local intradermal injection of chaulmoogra preparations, mild inflammatory changes, with fibrinous exudate, monocytes, and a few polymorphonuclear cells were seen as well as yellow fat globules (chaulmoogra oil). These fat globules were present even several months after the injection.

Other Fatty Acids (than Chaulmoogra Oil): Other vegetable products besides chaulmoogra have received trials in the treatment of leprosy. Most of these crude or refined products are fatty acids or their

esters. Some of the chief ones tried will be mentioned briefly.

Gurjun oil, from the "gurjun tree", found in India, was given orally and applied locally to the skin lesions, but it proved of no value.

Beautherpy, in Venezuela, in 1871, had his own "treatment" consisting of the application to the skin lesions of Cashew nut oil (also, he used caustics, such as silver nitrate). The treatment was used even as far away as in Mauritius, but it soon fell into disrepute, for no benefical results were produced.

Eucalyptus oil, in the form of external applications, likewise had no effect on leprosy.

In Central America and northern South America, the bark of the red mangrove of the genus *Rhizophora* was used orally in the form of an alcoholic extract, one teaspoonful twice daily. The dose was gradually increased to 8 or 12 teaspoonsful. Only temporary symptomatic relief occurred.

In Brazil, esters of the oil of the tree *Carpotrochea braziliensis* were given to lepers. In the Fiji Islands, ethyl esters extracted from the oil of the palm tree *Calophyllum bigator* were injected intramuscularly, once weekly, 5 to 8 c.c. per dose. Joint and nerve pains were relieved, and Neff, who used this oil, claimed that if the treatment was combined with chaulmoogra ethyl therapy, this combination of drugs was more effective than chaulmoogra alone.

Ichthyol, creosote, chrysarobin, resorcin, and pyrrogallel have all been applied locally to leprous lesions. Inflammation of various degrees and even sloughing of the skin was produced. With milder degrees of inflammation, the local circulation was improved. This improved circulation apparently produced any beneficial effects therefrom (slow resorption of some of the lesions).

Rogers, in 1920, suggested that the action of chaulmoogra oil was due to its unsaturated fatty acid content. He, therefore, used other unsaturated fatty acids, and injected them intramuscularly. These oils can be divided into four groups: (1) Highly unsaturated fatty acids; cod liver oil, the sodium salt of which was called sodium morrhuate by Rogers, was praised by him but later found to be too irritating for prolonged use. (2) Moderately unsaturated fatty acids; the ethyl esters of soya bean were shown to be very irritating and thus unsuitable for trial in leprosy. (3) Slightly unsaturated fatty acids; plain olive oil and ethyl esters of olive oil produced slight improvement in 25 per cent of patients in one series. (4) Almost saturated fatty acids; in this group coconut oil, plain and esterified, ethyl stearate, and ethyl margarate have been placed. They have no effect on leprosy.

During World War II, when it was impossible to obtain chaulmoogra oil from India, Degotte, in the Belgian Congo, substituted citronella oil. It was injected intramuscularly once a week, from 1 to 3 c.c. per dose, given for a period of 10 weeks followed by a therapeutic rest of two weeks. Degotte wrote that the results he obtained were as good as those he had noted with chaulmoogra oil.

Arsenical Compounds: When Ehrlich, in 1909, discovered salvarsan, the Wassermann test, published in 1906, was already known. Since many lepers give positive Wassermann (and Kahn) reactions, it was thought that salvarsan might also be effective against leprosy. The positive syphilitic serology is present in lepers free from syphilis and yaws and represents an unknown non-specific reaction. After trial of "606" in a number of small series of leprosy patients, Ehlers,[19] Gioseff,[20] de Vertenil,[21] Wellman,[22, 23] Sandes[24] and Montesano,[25] all expressed complete disappointment in this drug as related to the treatment of leprosy. Since 1912 it has not been used.

Mercurial Compounds: Around the turn of the century, when syphilis and leprosy were confused, so-called "syphilitics" who later turned out to be lepers were sometimes treated with mercuric perchloride, one intramuscular injection of 1/5 gr. per week. Two nerve-type lepers treated by Crocker showed only slight improvement. (For a discussion of the organic mercurial compounds, see under "Aniline Dyes"). Mer-

curial compounds have been dropped from the list of antileprotic drugs.

Antimony: In 1921 Cawston gave intravenous tartar emetic (2 per cent solution) in doses of 2 to 5 c.c. bi-or tri-weekly. He reported several instances in which leprous ulcers healed and anesthetic skin areas became hypesthetic. He also used colloidal antimony (oscostibium), giving it intravenously in bi-weekly doses up to 12 c.c. Wildish[26] reported on these drugs after two months' use and noted "encouraging decrease in size of ulcers" and lessening of anesthesia. Hoffmann suggested stibosen as an adjunct to chaulmoogrates. Rodriguez gave 1 per cent tartar emetic to 31 patients intravenously for six months, observed no improvement. His dosage ranged from 0.5 to 2.5 c.c. per week. Paldrock also, after a small clinical trial found fuadin without any effect.

At the National Leprosarium, 5 gm. intravenous fuadin are given to alleviate acute lepra fever, and the drug is found to be of value; often it ends the reaction within one day (personal communication).

Copper Salts: Cyanocuprol, after its beneficial effect was demonstrated in experimental animal tuberculosis, was tried on lepers in Japan by Kroga, also by Takano. They noted some softening and shrinking of nodules. Trocello showed that the drug produced fibrosis and lymphocytosis in experimental tuberculosis. Dho, in Italy, tried cyanocuprol, 2 per cent solution, given intravenously daily, on 20 patients. In the lesions he found proliferation of fibrous tissue and granulation of lepra bacilli. Many nodules became smaller in one to two months, but none of the patients became "arrested".

Gold Salts with Carbon Dioxide Snow: Gold salts were first used in leprosy by Dehio in Esthonia in 1914. In 1926, Paldrock, also in Esthonia, theorized that if leprosy bacilli were frozen, antigens should be set free and antibodies would be formed by the body and leukocytes mobilized in response to these antigens, and immunization thus obtained. He applied the carbon dioxide locally to the skin and reported five patients discharged as "well" after two years of such treatment.

The carbon dioxide snow is applied monthly for three to four seconds to each of ten lesions. After four monthly treatments the patient gets a therapeutic rest for four months. The carbon dioxide, Paldrock further postulated, stripped the bacilli of their capsule, and then these "denuded" bacilli could be attacked by heavy metals. Sanocrysin, a gold salt, proved to be a failure. Solganol, given concomitantly with carbon dioxide snow, produced lymphocytosis. Krysolgan, given by Eubanas to ten patients, showed "unequivocal results" after six months. It was administered as 0.0001 gm. intravenously, repeated at 10 day intervals. Triphal, another gold salt, gave no improvement.

Hoffman pointed out the value of gold salts in lepromatous ocular lesions to promote resorption. Kupffer observed small rises in temperature shortly after gold salt injections. He gave an initial dose of 0.001, later increased to 0.01, then 0.02 gm. every eight days. After three years, corneal, iris and fundal lepromata had disappeared.

Solganol has been administered in doses of 0.1 to 0.5 c.c. intramuscularly once to twice per week. The patients so treated were much too few in number to make any conclusions of value. Gminder was not successful with solganol. Pooman and Amies, however, reported marked improvement in about half of their patients. Lopion, a similar gold salt, was administered weekly by intravenous injection.

Golorine, writing in 1940, reported that he found toxic reactions so numerous with the use of the gold salts (skin eruptions, agranulocytosis and aplastic anemia) that he stopped using them. He found "aurodetoxin" not toxic and reported the beginning of a series of treatments with this compound. It was administered bi-weekly intramuscularly, with 0.05 gm. increased to 0.5 gm. weekly until 5.0 gm. were given.

Paldrock, in an article in 1933, modified and extended his former theory on the action of carbon dioxide snow and gold salts on leprosy. He reasoned that the differ-

ences between tubercle and leprosy bacilli consisted in: (1) a greater amount of free nucleic acid and karyoproteids in leprosy bacilli; (2) more firmly combined plasteoproteids in leprosy than tubercle bacilli, and (3) the presence of lipoproteid with Gram-positive and Gram-negative lipoacid lacking in tubercle bacilli. Paldrock therefore postulated that the leprosy bacilli actually contained nuclei, similar to fungi, and had a surrounding membrane. In fact, he considered the organism to be a fungus. Therefore, if this membrane could be removed, the nucleus would become accessible to antibodies. The colloids of the membrane should be broken down by freezing (with carbon dioxide snow). Polymorphonuclear proteases and lymph lipases then destroyed the remaining membrane colloids and the "nuclei" of the bacilli. Leukocytosis was marked. "Carbon dioxide snow treatment of leprosy is an active autoimmunization and therefore a specific remedy in leprosy."[27] If there was a standstill of improvement after two years' of snow treatment, Paldrock then used the gold salts as a new irritant. These salts, he believed, split the Gram-positive lipoid acid.

Only Paldrock and his associates have attained any success with this treatment. Its efficacy is not subscribed to by any other investigators.

Nastin: In 1904, Deycke and Reschad Bey cultured some acid-fast bacilli from human leprosy tubercles, ether-extracted the organism. The fatty portion, when injected in several lepers, had a beneficial effect. This substance was found to be a fatty acid glyceryl ester, melting at 48° to 50° C. Deycke called it "nastin." When injected in patients, nastin gave a pronounced leukocytosis in those who reacted, leukopenia in those patients who did not react. There was also local inflammation and fever. When injected with cinnamon acid nastin produced no leukocytosis. The authors therefore concluded that the leukocytosis was not necessary but that the organism used the leukocytes to gain the active agent from the above acid (found in balsam of Peru). In the body, the acid is oxidized by benzoic acid, but the latter is inactive. Therefore an intermediate compound, benzaldehyde, was used. Deycke and Reschad Bey concluded that the benzoyl radical was the substance which activated nastin. Benzoyl chloride easily splits off the benzoyl radical. Therefore, it was dissolved in olive oil with nastin. Without nastin, benzoyl chloride is of no value, since it will probably combine with other fats long before it reaches the lepra bacilli. Nastin will be more effective if combined with benzoyl chloride, for then it will not have to depend on the leukocytes to obtain the benzoyl radical. Once thus defatted, the bacilli are easily destroyed by the body.

The ration of nastin and benzoyl chloride is important, according to Deycke. If an excess of nastin is present, the patient has severe fever reactions and local inflammations with suppuration. Such reactions are not found if there is an excess of benzoyl chloride. Rather, leprous nodules slowly recede, and several patients with nerve type lesions had some regression of skin anesthesia.

The proper ratio is nastin, one part and benzoyl chloride, 30 parts or more. Deycke was convinced that with this treatment the patients became immunized. The combination of nastin and benzoyl chloride was called nastin B. For administration, a dry syringe is necessary (or, if the syringe is wet, the benzoyl chloride will form hydrochloric acid, and necrosis at the injection site occurs). Treatment is begun with nastin B_1 (an excess of benzoyl chloride), 4 c.c. containing 0.5 mg. once a week, later given more frequently. Nastin B_2 (excess of nastin) is used in small lesions resistant to nastin B_1. Reactions occur. It should therefore not be used in nerve leprosy or in leprotic eye involvement.

In small groups of patients with nodular leprosy, Kupffer, Ziemann, T. S. B. Williams, Rudolph, and Scott had good results (marked regression of nodules) in five to ten months of treatment. McLeod, Thompson, Brinckerhoff, and Kiwull in similar small series of patients got only febrile re

actions and local inflammations but no distinct improvement of their patients.

In 1909, Deycke went to the Government Leper Colony in British Guiana to initiate his nastin treatment in 503 patients there. He reported improvement in two-thirds of the nerve type, two-thirds of the nodular type, and two-thirds of the mixed type of leprosy patients treated. After four months, Deycke left Guiana to return to Germany. In a follow-up report three and one-half years later, the local Guiana leprologists, Wise and Minett, reported that of 250 patients still being treated by nastin, only four "cures", were recorded and one of these patients had meanwhile died and another had a recurrence of the disease. Wise and Minett reported that in the first three to six months of treatment mental improvement, better appearance of the facies, softening of the nodular lesions, slight decrease in the size of the infiltrations, and a slight increase in sense of touch in anesthetic skin areas occurred. However, improvement then stopped, and regression occurred in the next few months to the original pre-treatment state.

Tuberculin: Koch, in 1890, electrified the medical world with his discovery of tuberculin, a filtrate from glycerol-broth cultures of human tubercle bacilli. He advocated it as a possible immunizing agent against tuberculosis and tried it in the treatment of tuberculosis (with no success, as later became apparent). *M. leprae* being similar to *M. tuberculosis* in structure, several leprologists decided to try tuberculin in the treatment of leprosy. Goldschmidt found that seven of his twelve patients got severe febrile and local reactions from injection of 1.0 mg. of tuberculin, and the other five showed no improvement. V. Babes, treating five patients, also noted severe febrile reactions. His patients showed slight temporary improvement after the febrile reaction. Truhart's report was similar to the other two. Use of tuberculin in the treatment of leprosy was abandoned.

Rou, in 1926, gave weekly injections of 0.25 mg. autolysed tubercle bacilli, noted a mild febrile reaction. In five patients, two had resorption of nodules in one and one-half years of treatment.

Davidson injected tubercle endotoxoid in ten lepers, observed no improvement in nodular type patients but improvement of anesthesia in those with the nerve type of leprosy.

Bacterial Vaccines: In 1896, Carasquilla inoculated a goat with leper serum, later bled the goat, and injected the goat serum in fifteen patients, beginning with 0.5 c.c. and increasing the dose to 20 c.c. after one month. Eight to twelve injections, extending over six weeks, "cured" all of these patients, (nodules and anesthetic spots disappeared). No other investigator has ever been able to repeat Carasquilla's work.

Rost cultured an acid-fast bacillus from leprous lesions, injected it in a monkey and recultured an acid-fast bacillus from skin nodules on the monkey. This culture material he injected into ten patients with maculo-anesthetic leprosy, six of whom were "improved." Injections were given weekly in amounts of 5 c.c. of the sterilized culture material. After one year of treatment, five of twenty-two patients had recovered, fifteen were improved; two-thirds of these patients had the maculo-anesthetic type, the others the nodular type of leprosy.

Temporary improvement (softening of the nodules) in nodular leprosy was reported by Kraus in 1923 following local inflammation subsequent to the injection of acid-fast bacilli grown in culture by Duval and Deycke. Of nineteen patients, two showed this beneficial action. Walker, Hasson, A. W. Williams and Gohar, reported series of a few patients treated with similar vaccines and recorded only temporary decrease in size of nodules with softening but no permanent cures. Reenstierna, in 1936, treated a total of ninety patients in Venezuela and Colombia with a vaccine prepared by him from an acid-fast bacillus culture. Unfortunately, he observed the results for only three months. In two to four weeks the nodules softened, decreased in size. Eighty-seven per cent of patients with anesthetic skin areas had a partial return

of sensation. The course of treatment consisted of three injections of 10 c.c. each in one week.

In 1921, Roussel, of New Orleans, upon the suggestion of Campos, used anthrax vaccine in the treatment of two patients. It was given subcutaneously, beginning with a 0.25 c.c. bi-weekly dose increased to 1.5 c.c. in five weeks. The local lesions became inflamed, later disappeared completely within two months. In 1935, these two patients, who had the maculo-anesthetic type of leprosy, were still living and healthy.

Protein Shock Therapy: It may be argued that nastin, anthrax vaccine, and other bacterial vaccines should have been discussed under this title. However, since the users of these drugs have not claimed their action to be due to the febrile reaction which often attended their application, I have classified them separately. The substances mentioned below, however, act by producing febrile reactions.

Snake venom has had small trials in the treatment of leprosy. According to ancient Hindu mythology, a leper bitten by a snake is cured. In 1892, Carreau reported the case of a leper bitten by a venomous snake whose tuberculoid lesions disappeared. Dyer, of New Orleans, treated five patients with cobra antivenene. He began with 1 c.c. injected subcutaneously every other day, increased the dose to 10 c.c. every day. The lesions markedly diminished in size in all the patients in one to two months' time. Woodson and de Moura reported similar beneficial results. Goldschmidt emphasized that it was the febrile reaction produced by the administration of the venom which was probably responsible for the effect on the disease. Lewin went a step further and expressed the opinion that the injection of any foreign protein would produce a like result. Couhan, in 1938, found cobra venom effective in alleviating peripheral neuritis of leprosy in 60 to 80 per cent of his patients.

Erysipelas toxin, given in slowly increasing doses, proved of no value.

Typhoid-paratyphoid A-B injections also produced severe fever with temporary remission of leprosy afterward.

Injections of sterile milk, starting with a dose of 0.5 gm. increased up to 10 c.c. intramuscularly twice weekly were given by Drew to 36 patients, of whom he was able to discharge seventeen. Dyce-Sharpe also used it. Sarkar wrote that milk injections gave relief from neuralgia and joint pains of leprosy. Gomes likewise observed a diminishing in size of nodules and tuberculoid lesions in a series of 33 patients after one month of milk injections.

Iodine: Iodides (sodium and potassium) were first used by Danielssen and Boeck in Norway in 1848. They discovered that severe febrile reactions occurred in the patients thus treated. Diesing and Courtney (1900) used iodoform in olive oil, reported no reactions. In 1908, Marchoux and Bourret observed that lepra bacilli were discharged from the nose during such a reaction. They looked granular and had lost some of their acid-fastness. Several investigators, especially Rogers and Muir, noted a clinical improvement after such a reaction. Muir, in 1923, began his work on the iodide treatment of leprosy. He controlled the febrile reactions produced by the iodides by administration of tartar emetic (intravenously) and the painful symptoms of subcutaneous adrenlin injections.

Iodide reactions are considered harmful by many leprologists. Muir, however, considers them beneficial if the dosage is well-regulated. Iodides cannot be used in mass treatment; their dosage must be individualized. Muir begins with a small dose and slowly increases it to tolerance. Iodides are especially good to break down large amounts of lepromatous tissue, and immunity is thus increased. Signs of a reaction are:

(1). Swelling and erythema of the lesions.

(2). Appearance of fresh nodules, often painful.

(3). Fever.

(4). Markedly increased sedimentation rate.

(5). Granulation of bacilli.

Potassium antimony tartrate (0.02 gm. intravenously every other day) controls the reaction; 0.3 c.c. adrenlin in 3 c.c. saline (intramuscular or intravenous) stops the nerve pains. Muir suggested the following potassium iodide dosage:

(1). Begin with 1 gr. per day and increase it by 1 gr. until the temperature rises above 99.0° F., or there is swelling and redness of the lesions.

(2). When the swelling and fever go down, continue on the same dosage but give only once or twice a week.

(3). When 20 gr. are reached, increase the dosage by 5 gr.

(4). When 60 gr. are reached increase the dosage by 30 gr.

Iodides were used by Muir in the diagnosis as well as treatment of leprosy. Lepers showed a febrile reaction when given iodide. "The action of the iodides in some way removes the protective mechanism which shuts off the bacilli from the tissues."[28] Only lepromatous patients in good general health who will be able to withstand the strain of the febrile reaction should be treated with iodides.

Canaan explained the iodide reaction to be due to killing of many bacilli, whose toxins then entered the blood stream; nodules break down, and a bacillemia is produced. Canaan abandoned the iodide therapy and agreed with Cochrane, who wrote: "When iodides were introduced it was hoped that they would hasten the resolution of the disease, but in my experience patients treated with potassium iodide showed no more rapid subsidence of their leprotic infection"[29] (than those treated with chaulmoogrates).

Aniline Dyes: Aniline dyes have been used as antiseptics since the turn of the century. In 1929, Hoffman used rivanol, an acridine dye, as a powder in open leprous lesions. Several such lesions healed up over a period of three months. Hoffman therefore thought that it had some beneficial action but ascribed this action to destruction of secondary invaders rather than lepra bacilli.

Denny and Muir found the intravenous administration of mercurochrome effective in treating lepra reactions. Ryrie, working in Malaya, thereupon speculated that the abortion of lepra reaction with mercurochrome was due to its fluorescein content, and the fluorescein was taken up by the macrophages in the leprotic lesions and interfered with the process deriving from the attachment of antibody to the cells. He preferred to give fluorescein to mercurochrome, because the former could be given safely in much larger doses. He gave 10 c.c. of 2 per cent aqueous solution intravenously twice a week. The lepra reaction stopped in 24 to 48 hours in 42 per cent of the patients. The others had remission in two to three weeks, and in this time, according to Ryrie, the reaction would probably have ended spontaneously. In a subsequent series of patients, Ryrie injected intravenously phthallic acid, the active ingredient of fluorescein. In 62 per cent of the patients, the lesions decreased in size in two months. Ryrie therefore suggested a course of six weeks fluorescein between courses of chaulmoogra esters.

Ryles noted the sensitizing action of aniline dyes to the skin to enhance the effects of ultraviolet rays. He hoped this combination of ultraviolet ray enhancement and antiseptic properties would show the dye, brilliant green, useful in leprosy therapy. He sprayed the dye (1:10,000) on leprous ulcers. The ulcers readily healed. Then he gave the dye intradermally, and two-thirds of his 455 patients so treated improved. The dosage used was 5 to 8 c.c. of 1:2,500 solution with 1 per cent novocaine given once weekly, then given two weeks' rest. Ryles found "Bonney's blue" even more effective than brilliant green. Bonney's blue consists of:

Brilliant green powder	0.5 gm.
Crystal violet	0.5 gm.
Absolute alcohol	25.0 c.c.
Distilled water to	2500 c.c.

The crystal violet is added to the alcohol, then added to the rest.

Legate also noted considerable regression of lesions in ten patients with nerve type leprosy after several months' treatment with Bonney blue.

Rao and Roy found Bonney's blue, brilliant green, trypan blue, and fluorescein ineffective in their patients.

Emerson et al., in 1934, investigated the activity of the aniline dyes *in vitro* on various acid-fast bacilli and found them all (merthiolate, mercurochrome, metaphen, methylene blue, octyl resorcinol) quite active except trypan blue. They also showed that severe nephritis was produced by these dyes in experimental animals and therefore cautioned their use in lepers, since nephritis is one of the complications of leprosy. Nausea and vomiting also occurred in clinical cases.

Montel, in 1934, treated a few patients with intravenous methylene blue. His "successes" were later withdrawn when a second larger trial gave no beneficial results. In 1940, Dharmendra found that methylene blue carried no effect on rat leprosy nor *in vitro* cultures of acid-fast bacilli.

Since then, no reports of any further work with these dyes have been published, for they have not proved themselves of value.

VITAMINS

Thiamin chloride (vitamin B_1) has been reported on in the treatment of nerve leprosy by several authors. Muir and Henderson noted that rat leprosy was often accompanied by hypovitaminosis and that B_1 had a pathogenic and therapeutic relationship to nerve leprosy, and they showed that rat leprosy could be more readily induced in animals in the presence of hypovitaminosis. Vitamins A and C had no effect, but the B group had a definite relationship to this phenomenon. Badger and Sebrell showed that vitamin B_1 was responsible.

Brown, in Nigeria, treated 66 lepers with addition of yeast to their diet, later injected vitamin B_1 intramuscularly and noted "improvement in 43 per cent" of these patients. He pointed out the poverty of B vitamins in tropical diets. Bacu noted improvement of nerve pain and lessening of skin anesthesia after four weeks of yeast administration. Bacu emphasized the clinical similarity of nerve leprosy and beriberi (peripheral neuritis, muscle paralysis, trophic disturbances). Another interesting speculation of his concerns the higher intake of carbohydrate in the tropics with therefore greater vitamin B_1 demand for metabolism of these carbohydrates. Beriberi is most common in the tropics. Also in the tropics the nerve type of leprosy is much more frequent than the nodular variety, which latter is seen in the majority of lepers living in the temperate zones. Bacu gave 5 to 10 mg. thiamine chloride (subcutaneous or intramuscular) daily, observed improvement of neuralgia in nerve lepers after two to three weeks. A diet with yeast, unpolished rice, wheat germ, green vegetables to furnish vitamin B_1 was introduced.

Villela, Badger, Gminder, Bleuth, and How, also were able to alleviate acute peripheral neuritis in leprosy with thiamine injections, but they all agreed that none of the other symptoms of leprosy were relieved. How suggested that vitamin B_1 deficiency may predispose to nerve injury by the lepra bacilli.

DIPHTHERIA ANTITOXIN AND TOXOID

In the middle 1930's Oberdoerffer, a German leprologist, read of some work done by A. Clark, who had drawn attention to certain toxic properties of colocasia (or cocoyam or taro root, a food plant of the genus *Xanthosoma*, usually species *sagittifolium*). Clark ascribed the general debility of taro-fed people to these toxic properties, residing in an acid sapotoxin. Acute poisoning with colocasia, he found, produced "glomerulo-tubular nephritis and marked degeneration of the adrenals". The sapotoxin, he discovered, hemolyzed blood *in vitro*. He also demonstrated that the highest degree of toxicity of the plant occurred at the end of the dry season. Instantaneously killed animals showed marked adrenal degeneration. This adrenal destruction Clark considered the immediate cause of death.

Oberdoerffer, working in Nigeria, noted that nerve leprosy most often cropped out

at the end of the dry season, the time when the native people ate the most colocasia. He then proposed the theory that adrenal damage, as for example caused by colocasia consumption, predisposed to leprosy. With this idea in mind, he searched for an "adrenal-protecting" substance. Since diphtheria toxin destroys the adrenal, the antitoxin, he argued, must have a protective power. Therefore, when he went to the Siam Leper Colony in 1938, he, Collier and McKean treated a group of patients with 6,000 units of diphtheria antitoxin for forty daily doses. Later, 2,000 unit injections were given every tenth day. They noted decrease in and flattening of the nodules, often scaling over, and gradual shrinking. Tetanus antitoxin had no such effect.

Next, Oberdoerffer and his associates tried a group of patients on diphtheria toxoid and again observed the shrinking of the nodules after two to four weeks of treatment. The nerve leprosy patients had a reduction in size of their enlarged nerve trunks and partial return of sensation of anesthetic skin areas. Fragmentation of bacilli in the lesions occurred. The dosage of the toxoid was 1 c.c. every two weeks, increased by 0.5 c.c. until a maximum of 3 c.c. was reached. Fifty per cent of the patients became symptom-free (78 patients) in ten months and were discharged. McKean reported that better results were obtained in the nerve type than in the nodular type of leprosy.

Other investigators—Schujman and Mercau, Moiser, Davison and Grasset, found the diphtheria toxoid ineffective. Carpenter et al. found it had no effect on rat leprosy. Muir suggested that Oberdoerffer, Collier, and McKean got such spectacular results because they mistook early tuberculoid for lepromatous lesions and were therefore merely observing numerous spontaneous recoveries from leprosy, often seen in early tuberculoid nerve type.

In a personal conversation with Dr. McCoy, he recalled a meeting he had with Dr. Collier in which the latter showed him photographs of the "before" and "after" appearance of these Siamese lepers treated with diphtheria toxoid. Dr. McCoy could see no difference in the pre- and post- therapeutic pictures and thought that Dr. Collier had been so influenced by his own enthusiasm for the treatment that perhaps, in being partial to it, he had almost "imagined" improvement where an impartial observer could see none. Dr. McCoy then devised a controlled experiment, with one-half of the patients receiving *placebo* injections, judged by himself for results (he assuming the role of an impartial observer) to be run for one year at the Carville Leprosarium. The results were summed up by Faget and Johansen: "From close observation of 35 patients treated with diphtheria toxoid for one year under carefully controlled conditions and from the observations of 195 other patients treated with diphtheria toxoid from six to fifteen months, it is concluded that this treatment has no beneficial therapeutic action in leprosy and is even fraught with danger to the patient."[39]

SULFONE DRUGS

In the early days of sufonamide drugs, prontosil and soluseptacine, the latter given in intramuscular injections of 5 to 10 c.c. each, were shown to clear up secondary infections but to have no effect on the lepra bacilli themselves.

Sulfanilamide, given in doses of 2 gm. per day for six weeks at the Carville Leprosarium, was adandoned. Its administration was accompanied by anemia, drug fever in over one-half of the patients, lepra-reactions, and conjunctivitis. There was no apparent effect on the leprosy itself, but secondary infections healed. In rat leprosy sulfanilamide had some beneficial effect, for Krakower found that he could inhibit the disease in all his animals with this drug, but the disease reappeared as soon as the animals were taken off sulfanilamide. Krakower's conclusion therefore was that sulfanilamide is bacteriostatic rather than bacteriacidal in action on *M. leprae*.

Promin, a sulfone drug, was first used in leprosy in 1941. It is called Na salt of p,p^1-diaminodephenyl-sulfone-N,N^1-di-(dextrose sulfonate).

W. M. Simpson was the first to suggest that it be tried to influence the regression of rat leprosy nodules. After this work was started, Feldman, Hinshaw and their associates at the Mayo Clinic reported that tuberculous guinea pigs treated with it lived longer and showed less extensive lesions than the controls. Condry noted similar hopeful signs in a series of rates inoculated with rat leprosy.

Hinshaw and Feldman treated 36 pulmonary tuberculosis patients with oral promin over one year's time. Eight patients (20 per cent improved markedly, 14 (38 per cent) slightly, eight (20 per cent) remained stationary, and eight (20 per cent) became worse. The series was too small to evaluate promin in the treatment of tuberculosis, but Hinshaw considered this result somewhat encouraging.

At the Carville Leprosarium, promin treatment was begun under the direction of Faget in 1941. Because the oral administration of the drug (1/2 to 1.0 gm. per day) soon produced severe hemolysis and anemia, intravenous injection was tried. One to 5 gm. per day for six days per week were given. Most patients tolerated the 5 gm. dose. One week out of three the patients "rested" (no promin was given). Promin blood levels decreased rapidly, so that only traces of the drug remained after six to eight hours. Toxic manifestations appeared after about six weeks of treatment. The most important ones were a slow erythrocyte destruction. A blood count must therefore be done twice a month. In 71 per cent of the patients erythrocyte count fell below the 3,500,000 mark, below 3,000,000 in 9 per cent. Antianemic treatment was successful in most cases, and the promin did not have to be stopped. Oral iron and liver extract were effective in controlling the anemias, but occasionally an anemia was so severe that it was necessary to give oral iron and parenteral liver extract. When the erythrocyte count dropped below 3,000,000 promin was stopped temporarily while the iron and liver extract were given and later cautiously resumed in reduced (1 to 2 gm.) doses.

Leukopenia occurred in 3 per cent of the patients. There were no urinary disturbances, but because nephritis can be caused by sulfonamides, urine examinations were done every two weeks. Other toxic reactions included maculo-papular dermatitis in 16 per cent of the patients. Desensitization (beginning with 0.1 gm. and increasing the dose to 2.0 gm. over a two month period) was successful. Allergic rhinitis, headaches were less common complaints. Nausea occurred in 35 per cent, could be prevented by injecting the drug slowly. Acute lepra reactions were less frequent than they had been with any other previous form of treatment. A few patients had exacerbations of iridocyclitis followed by improvement.

Of 68 patients, most of whom had moderate or advanced lepromatous, mixed or nerve leprosy, 41 (60 per cent) were improved, 23 (32 per cent) stationary, and four (8 per cent) worse. "Control" patients were definitely in poorer health. "Promin is an advance in the right direction", Faget et al. wrote.[31]

In a follow-up report in 1945, Faget and Pogge noted "continued improvement" of the patients observed earlier. There were now 137 patients under promin therapy, of whom 80 (58 per cent) were improved. Those under treatment less than six months only showed 26 per cent improvement. Those under treatment showed an improvement rate of 71 per cent. Sixty-two patients on promin more than one year had a reversal of bacterial skin smears from positive to negative. Certainly, the authors concluded, the drug is more beneficial than anything else tried so far. Whether its action is chemotherapeutic remains to be seen. Faget (personal communication) believes 25 per cent of patients will improve in the first year of promin therapy, 50 per cent in the second, 75 per cent in the third, and 100 per cent in the fourth.

Fite and Gmear studied the skin biopsies of patients treated with promin at the Carville Leprosarium. They reported: "The important finding is that promin appears to eliminate bacillary infections of the blood vessels and blood stream, thereby pre-

venting the formation of new lesions. Those lesions with the richest blood supply show most atrophy. A more powerful bacterial agent than promin appears to be necessary for the chemical destruction of bacilli within tissue cells, and especially those within globi."[32]

Wharton, who observed great improvement in seven advanced type lepromatous patients, found that the lepromatous tissue after treatment became fibrous connective tissue. Wharton theorized that the destruction of lepromatous cells makes it impossible for the bacilli to multiply.

Smith, McCloskey and their associates, ran an interesting chemotherapeutic experiment with combined streptomycin and promin in guinea pigs infected with human tuberculosis. They calculated the therapeutic index of streptomycin against tuberculosis to be ten times as great as that of promin. By combining the two drugs, they obtained an effect three times as great as they had expected. Therefore they wrote: "The results of treatment with the combination of streptomycin and promin appear to indicate a synergistic action rather than simple summation of effects."[33] This observation may prove to be of interest in future investigations on the effect of these drugs in leprosy.

Another sulfone drug now being used in the treatment of leprosy is diasone. This is the disodium formaldehyde sulfoxylate derivative of diaminodiphenyl sulfone. It was first synthesized in 1937. Callomon, in 1943, reported that it inhibited the progress of experimental tuberculosis in guinea pigs and was less toxic than promin. Feldman's observations were similar. Petter and Prenzlau found it useful in clinical human tuberculosis. They treated 108 patients with 1 gm. per day, given orally. The blood levels averaged 2 mg. per cent. Toxic reactions consisted of headache, malaise, gastric upset, and mild anemia. Almost all the patients "improved", even those with far-advanced tuberculosis. Olson, in 10 tuberculous patients treated for one year, noted no improvement.

At the Carville Leprosarium, Faget et al. began the use of diasone in 1944. They began the treatment with 1/3 gm. given orally three times a day but found that several patients developed a hematuria. Then the beginning dose was reduced to 1/3 gm. per day and increased to 2/3 gm. in two weeks and 1 gm. in three to four weeks. Over a two and one-half year period 104 patients were treated, of whom 66 have been on diasone six months or longer. Seventy-four per cent had the lepromatous type, 20 per cent mixed, and 6 per cent neural leprosy. In 81 per cent the disease was moderate to advanced; 24 per cent of the patients became bacteriologically negative; improvement was present in 65 per cent; questionable improvement in 12 per cent, and no change in 23 per cent. None of the patients became worse. Treatment had to be discontinued in 30 per cent because initial hematuria, eczema or vomiting occurred. Diasone is about as effective as promin in leprosy, according to Faget, and has the advantage of being an orally administered preparation. Muir observed an increased tolerance with continued diasone administration accompanied by a decreased bleed level. Perhaps, he suggests, that is why anemias occur only rarely after the initial administration. Smith, in 1943, found a lowering of threshold of renal secretion of diasone in experimental animals. This may be a factor in lowering blood levels. If this is the mechanism involved in lowering the blood levels, it is necessary to find out what period of non-administration is necessary to restore the original blood level.

Promizole, another sulfone drug, 2,4'-diamino-5 thiasolphenyl sulfone was also tried in experimental tuberculosis. The results were the same as with promin. However, there were no toxic reactions, but the animals' thyroid gland became diffusely enlarged. Hinshaw gave 10 to 16 gm. per day orally to tuberculous patients without toxic manifestations.

Promizole was introduced at the Carville Leprosarium in 1945 because it had given encouraging results in skin tubercu-

losis and also had been relatively non-toxic. Seven patients were treated for one year; eight for six months. The beginning dose was 0.5 gm. three times a day per month, slowly increased to 2 gm. three times per day. Improvement occurred in all the patients, but the skin smears were still positive for bacilli. Further trial is needed to evaluate the drug.

ANTIBIOTICS

Penicillin was tried on seven patients at the Carville Leprosarium in daily doses of 50,000 to 100,000 units for one month. When no beneficial effects resulted, the dosage was increased and the drug continued another month. Still, there was no effect. It was therefore concluded that penicillin had no influence on leprosy. In trials in Spain and Latin America similar conclusions were reached. It is, however, effective in controlling secondary infections.

Waksman and his associates found streptomycin, an extract from meat-broth (or corn-steep liquor) cultures of *Actinomyces griseus*, to inhibit growth of *in vitro* cultures of human and avian tubercle bacilli, in addition to other organisms. Since their report in 1944, several trials of the drug on experimental tuberculosis in guinea pigs have shown that the treated guinea pigs showed only minimal tuberculous lesions while control animals had multiple large lesions and usually died. Even after the disease had been allowed to progress for six weeks in one series, treatment begun at that time saved 23 out of 25 animals, while 17 of 24 controls died. In clinical tuberculosis, streptomycin has so far proved to be a "hopeful" drug, but experience with it is still too short to make evaluation possible. Feldman and Hinshaw treated 34 patients with 100,000 to 150,000 S-units intramuscularly every three hours. Those patients with fine, disseminated pulmonary tuberculosis showed much roentgenographic improvement after six to eight weeks. Urinary tract lesions cleared up in three out of four instances. Old, fibrotic lesions and cavities were not affected. There were several relapses after cessation of therapy. The authors, therefore, considered the drug bacteriostatic rather than bacteriacidal.

Since tuberculosis and leprosy are caused by similar organisms and have a number of pathogenic characteristics in common, it was only natural that streptomycin should also be tried in leprosy. Ten patients at the Carville Leprosarium were placed on 1 gm. intramuscular streptomycin six months ago. So far, no results have been published. Two months ago, on the writer's visit to Carville, he was told that there had been slight shrinking of some lesions of these patients, but no conclusions could at that time be drawn. The treatment, of course, is very expensive—about $1000.00 per patient per month. Only time will tell what the results will be. Most of the patients had the feeling of dizziness described under the toxicity effects of streptomycin and one also had transient nerve deafness. Several of these patients are being treated with both promin and streptomycin.

For the treatment of the trophic ulcers of leprosy a new method has been devised at Carville: streptomycin broth culture filtrate is applied as a wet dressing to these ulcers, and they have healed in a few weeks, whereas leprotic ulcers have always been more or less refractory to any treatment. Whether the streptomycin kills secondary invaders or inhibits the lepra bacilli themselves is not known.

Johnson and Burdon recently reported a new antibiotic, Eumycin, extracted from certain strains of *Bacillus subtilis*. It inhibits *M. tuberculosis* cultures (both human and avian) in high dilutions. It is now being investigated by Fite in experimental rat leprosy.

SUMMARY

There are some three million lepers in the world, most of whom are in India and China. The disease is only mildly contagious and is usually contracted after a long period of close contact with a leprous patient. Eighty per cent of lepers come from a home in which a leprous family member lives. The incubation is less than five years in four-fifths of the cases. The disease is caused by the acid-fast bacillus, *Mycobac-*

terium leprae. The principle clinical types are nodular (lepromatous) and nervous leprosy. The nodular type is more severe than the nervous, but both carry an unfavorable prognosis. Tuberculosis and glomerulonephritis are the two chief complications of leprosy.

Prophylaxis of leprosy has traditionally been conducted chiefly through segregation of leprous patients, and voluntary segregation has been most successful. The "general" treatment is the most important aspect of the therapy of leprosy. A diet especially rich in proteins and vitamins and well-supplied with carbohydrates and fats is important. Work and recreation must be offered in leprosy institutions.

Specific drugs are difficult to evaluate because the disease has such a prolonged course and sometimes remissions. Also, some patients exhibit more resistance than others and therefore may even spontaneously recover.

Chaulmoogra oil is the drug that has been most widely used in the treatment of leprosy. The oil is derived from trees of the family *Flacourtaceae*, in particular from the seeds of *Hydnocarpus* and *Taraktogenus* species. The oil formerly was used orally. Ethyl esters of the various fatty acids contained have been used most widely. They are given intramuscularly, subcutaneously, or intradermally. The sodium salts of these fatty acids have also been injected, especially intravenously. The mode of action, according to some authors, is due to the pentacycle carbon ring. Rogers, on the other hand, thought the effects were due to unsaturation of the fatty acids. Oral dosage produces nausea and vomiting, and local inflammation occasionally follows injection. The effect of the oil on the disease is almost impossible to evaluate from present reports. The International Leprosy Congress in 1938 considered chaulmoogra oil, and especially its ethyl esters "the most efficacious drug" then known. No specific effect was claimed.

Other vegetable and animal fatty acids have been largely discarded. Those used included sodium morrhuate, oil of eucalyptus and oil of citronella.

Various metal salts have been tried. The frequently positive Wassermann test suggested some relationship to syphilis, later proved to be false. Arsenicals were shown to be of no value, as was found to be true also of mercurials. The only antimony compounds still used are tartar emetic and fuadin, used to treat acute lepra fever. Copper salts have only been rarely tried. Paldrock froze the local lesions with carbon dioxide snow and then gave organic gold salts. He recommended the gold salts particularly in the treatment of leprous eye lesions. He claimed to have obtained numerous arrests of the disease.

Vaccines against leprosy have failed to affect the disease except in so far as they produced protein reactions. Nastin, tuberculin and various other bacterial vaccines are such substances.

Protein shock has been produced by snake venom, milk, erysipelas toxins and typhoid vaccines. All these give a more or less severe reaction. Any benefit obtained is derived from such reactions.

Iodine similarly gives marked febrile reactions.

Aniline dyes (mercurochrome, brilliant green, crystal violet) have been locally applied and injected intramuscularly. Severe toxic reactions with skin rashes and blood disorders were frequent, and the drugs were discarded. Thiamine only had one positive effect; it reduced nerve pain.

In 1940, diphtheria toxoid and antitoxin were acclaimed as specific against leprosy, but this was only a mistaken observation.

Sulfone drugs were first used in leprosy in 1941. Promin has been given to almost 200 patients at the Carville Leprosarium since that date, and the majority of these people had moderately to far advanced lepromatous leprosy. The results over these five years have been very encouraging, for almost all patients showed some improvement and about 40 per cent in one reported series had a reversal of the skin smear formerly positive for lepra bacilli. Advanced nodular lesions slowly resolved, and the patients noted a generalized improvement in themselves. The drug was described

as at least "the most beneficial of any drugs yet tried". Whether its action is chemotherapeutic is still a moot point. Toxic effects consist primarily of the production of anemia and more rarely skin rash. Because it proved to be too toxic when given orally, it has been injected intravenously. Diazone and promizole, two other sulfone drugs, have been given by mouth, and their effect on the disease was of about equal intensity to that of promin. The toxic effect was principally hemolytic anemia, occasionally skin eruptions and nausea and vomiting.

Several reports on promin and diazone from Latin America and Africa are quite as favorable as those from Carville.

Streptomycin has been begun on a small group of patients at Carville. No reports are yet available, but these patients have already shown some regression of lepromatous lesions.

CONCLUSION

Until 1941, only chaulmoogra oil had withstood the scrutiny of investigators sufficiently to be given the dubious title of the "most beneficial" agent known against leprosy. Since then, however, the sulfone drugs have, in the hands of several groups of leprologists, taken over this title. It now remains to be seen whether: (1) their action is specific against lepra bacilli; (2) they will cure early cases of leprosy; (3) other related compounds can be found whose effect is more pronounced and/or specifically chemotherapeutic; (4) streptomycin or another antibiotic yet to be discovered will be specific. It is certain that, though caution is necessary in ascribing antileprotic qualities to any drug, these recent developments of sulfones and antibiotics bring to the fore real possibilities that a true chemotherapeutic agent may soon be discovered.

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*Because of the length of the list of references (290) it is impossible to publish it in toto. Any one interested in consulting the complete bibliography may do so at the office of the Journal.

NEW ORLEANS
Medical and Surgical Journal

Established 1844

Published by the Louisiana State Medical Society under the jurisdiction of the following named Journal Committee:

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SUBSCRIPTION TERMS: $3.00 per year in advance, postage paid, for the United States; $3.50 per year for all foreign countries belonging to the Postal Union.

News material for publication should be received not later than the eighteenth of the month preceding publication. Orders for reprints must be sent in duplicate when returning galley proof.

Manuscripts should be addressed to the Editor-in-Chief, 1430 Tulane Ave., New Orleans, La.

THE JOURNAL *does not hold itself responsible for statements made by any contributor.*

FOOD CONSERVATION

The medical profession has been solicited to lend its support in the President's program to conserve food in our Country in order that the hungry and destitute people of Europe may be fed.

The prime problem and duty of the doctors is scientifically to assist and direct their patients and their families in trying to maintain a diet sufficient in calories and vitamins to sustain the individual in a healthy condition. The question of substitions for the meatless Tuesdays and fowlless Thursdays will need the dietary assistance of physicians and allied groups. Religious fasting and abstinence have accustomed most of our people to such a regime. Therefore to maintain this new order should not be such a difficult problem. We physicians should put forth the proper effort to assist in the successful handling of this regrettable emergency.

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STATE HOSPITAL SURVEY AND EXPANSION PROGRAM

In order to comply with the Hill-Burton Bill for survey and expansion of needed hospital facilities, the Governor of our State has caused to be set up a working committee to make a survey. This committee has been very busy for several months and it is understood that a tentative program has been perfected. The State Board of Institutions has been designated as the certifying agency for Louisiana. At a recent public meeting of interested agencies to hear objections to the proposed draft of plans, an inherent danger was brought forth. This is the possibility of establishment of a political bureaucracy in the state, which would control selection of the location, define the needs and supervise the expansion of privately owned hospitals as well as state institutions. It can well be understood what a distinct disadvantage would accrue if this is a fact and the injustice which would be inflicted upon physicians or lay people who own private hospitals and who would like to improve and expand their facilities by taking advantage of the provisions of the Hill-Burton Bill, and then have the disapproval of the certifying bureau, a political agency of the state. The great need for improvement in hospital and medical services should prompt the supplying of proper safeguards to prevent such from happening and thus assume an equitable supervision and assistance for these great humanitarian needs, free from any political strategy. It is hoped that the certifying agency will be conscious of such probable hardships and give their assurance to the end that same will be prevented.

WE MUST BE VIGILANT

In the October issue of the Journal under the Organization Section there appeared an appraisal of the recent report of the Subcommittee of the Committee on Expenditures in the Executive Departments, House of Representatives, Forest A. Harness, Chairman. There were cited in this report six agencies or bureaus of the Federal Government which were alleged to have spent illegally federal funds for the promotion of "Health Workshops" in various places of the U. S. for the purpose of fighting for Federalization of Medicine. The same group of individuals who for years have been fighting for the Wagner-Murray-Dingell Bills, was again performing in these workshops by lending aid and their presence to these meetings. What an expose! It really lifted the iron curtain and exposed their activities. This same group of proponents of national health insurance, although having so far failed to reach their objective in this country, tried in every way to have a similar piece of legislation made into law in Hawaii. Thanks to a diligent and strong medical profession these plans back-fired and again failed. Do you think they ceased their efforts to promote government insurance? Not by any means. They proceeded to tighten up their belts and by alleged devious means secured a request for them to go to Japan as supposed Consultants to General MacArthur (without knowledge of Army officials) on health and medical expansion. From correspondence intercepted it was learned that their chief function was to establish governmental health insurance for Japan, a defeated and prostrate nation. They thus proposed to help reconstruction on a plan which is not now applicable to the United States. How ironical! Read what Representative Harness says in a letter to Representative John Faber, Chairman of Committee on Appropriations, House of Representatives, as follows:

"I deem it proper to bring this matter to your attention because it appears to me to involve a question of legislative policy for the consideration of the Appropriations Committee. All members of this mission are permanent full-time employees of the federal government and are well known in the United States for their persistent agitation for a national system of socialized medicine to be achieved through a program of compulsory health insurance. The members of the mission are:

"Joseph W. Mountain, Associate Chief, Bureau of States Services, U. S. Public Health Service; Burnet M. Davis, Surgeon, U. S. Health Service; Barkev S. Sanders, Chief, Health Studies Division, Bureau of Research and Statistics, Social Security Administration, and Frances A. Staten, Assistant Regional Director for Management, Federal Public Housing Authority.

"This mission departed for Tokyo on August 28, 1947. We are informed that at a later date the mission will be expanded to include Mr. Arthur J. Altmeyer, Commissioner of the Social Security Administration; Mr. Wilbur Cohen, Assistant Director of the Bureau of Research and Statistics, and possibly Mr. I. S. Falk, Director of the Bureau of Research and Statistics."

From this record we find the same groups, bureaus and individuals at work which have been so prominent in the past in supporting governmental insurance in our country. We must therefore continue to educate our physicians, members of Congress, and the public—how subtle and low these determined employees of the government will stoop to reach their goal. They have millions and the government behind them. We must develop courage and determination to press our cause, for right is might!

ORGANIZATION SECTION

The Executive Committee dedicates this section to the members of the Louisiana State Medical Society, feeling that a proper discussion of salient issues will contribute to the understanding and fortification of our Society.

An informed profession should be a wise one.

THE ACTIVITIES OF THE WASHINGTON OFFICE OF THE A.M.A.*

JOS. A. LAWRENCE, M. D.†

For the director of the Washington Office, the day always begins with his scanning the morning papers—The Washington Post, before and during breakfast; and The New York Times, in the trolley, on his way to the office. The numerous news reporters, continually swarming through the Congressional halls and offices in their zealous search for news, uncover many doings and frequently discover early leads of actions contemplated by the Government divisions. The columnists' contributions must be scanned for references that may be made to proposed or pending health bills; also the column that reports what happened in Congress yesterday, and is to happen today, must be carefully read, and the names of the visitors who called on the president, noted. The morning mail which arrives at the office brings, in addition to correspondence, reports from two legislative reportorial services and the Congressional Record. Each in its way—and they differ somewhat in their fields of interest—will tell what happened "on the hill" the day before, and what the several calendars carry for today. We are particularly interested in learning whether any committees will hold hearings during the day on bills we are following and, if so, when they will begin and the rooms in which they will be held. The three legislative services report by title and number, the bills which were introduced in both houses the day before, and by whom sponsored. We study the list and check those to be followed and those to be read carefully. The same mail will bring printed copies of the bills introduced two days previously, and such committee reports as were released by the Government Printing Bureau. We have a contract with the Bureau to send to the office a copy of every bill, report, or resolution as soon as it is printed.

After hastily scanning the mail, it is turned over to the director's assistant to study more carefully, while the director hurries to the Capitol or respective office building, to attend such hearing as may be scheduled. Hearings usually begin promptly at 10:00—occasionally one may be advanced to 9:30—and terminate at 12:00 noon, at which time the two Houses convene. If the hearing is a very important one and cannot be terminated by noon, the Chairman may ask permission of the respective House to continue during the afternoon. If permission is granted, it is with the understanding that the members will come to the Chamber if a roll call or vote is demanded.

In the afternoon, we take up our work in the office—attending to our correspondence, reading and studying the bills, resolutions and reports that were received. We must be prepared at all times—but particularly in the afternoons—to answer, with the proper information, such telephone calls as may come from the Congressmen or their secretaries (especially the secretaries of committees considering bills in which we are interested) for occasionally a Congressman will leave the chamber while a bill is being discussed and call us for some specific information that he may need for the debate. Some afternoons we call at the committee rooms and discuss with the secretaries our attitude on bills they are considering. We like to hear from the introducer of a health bill what he considers the special merits of the bill he is sponsoring and arrange to call upon him at his office in the morning before ten or in the afternoon, either in his office or by calling him from

*Read before the Southern Regional Conference of the A.M.A., New Orleans, October 23, 1947.

†Director, Washington Office of the Council on Medical Service of the A.M.A.

the floor, as he may prefer. At their convenience, we call upon each member—beginning with the chairman—of the committees considering our bills, for the purpose of discussing the merits and scope of the several bills referred to them. These calls usually result in our being asked to provide them with specific information, relative to the professional aspects of the bills under discussion. We attend the sessions of the respective Houses when health bills are on the calendar for action.

Our attendance at hearings given health bills is very essential. Witnesses wishing to testify at hearings are required to submit to the clerk of the committee, several days in advance of the date set for the hearing, seventy-five written copies of their statements, in order that each member may have a copy to study in advance of the time it is presented. Extra copies are provided for distribution to the press, and others on the day of the hearing. These statements will all be printed eventually in the report of the hearings, but we immediately summarize each one or excerpt important paragraphs and report them in our bulletin, together with notes we collected while the hearing was in progress.

During the session, the office issues a bulletin at intervals of about ten days, in which is reported to a mailing list of over 1500 persons (mostly physicians) and organizations, the new bills introduced in the interval, such action as may have been taken on any bills previously reported, and the dates when hearings and conferences are to be held. Special bulletins are issued as necessary, in which are reported accounts of the hearings.

The Council has felt that there should be expressed in the bulletin, when important bills are reported, a statement of approval or disapproval, with explanatory reasons; and, at its request, the Board of Trustees has appointed a committee which will study each bill and instruct the director of the Washington Office as to the desirability of such legislation. These instructions will be promptly reported in the bulletin so that they may be used as a basis for conversation between a physician and his Congressmen.

In the office, a very careful file is kept for each bill reported in the bulletin. All correspondence relating to it and its subject matter, together with committee reports, newspaper clippings, and reports of discussions on the floor, are filed in one pocket and kept up to the minute. A cross index is maintained so that each bill is catalogued chronologically as introduced, as well as by subject and by name of introducer and sponsors. A file is also kept in which is recorded the name of each Congressman, his state, office number, names of committees or commissions of which he is a member, the bills he has introduced that interest us, and his announced attitude on health subjects. This information is also cross indexed, according to subject matter of bills introduced.

So much for Congress and its relations, but our work does not stop there. A more or less close relationship is maintained with all of the Government Departments and Bureaus that are engaged in administering the health and social security laws. The office receives regularly the newspaper releases and publicity material distributed by many of the Government departments, especially that issued by the Veterans' Administration, the Federal Security Agency, and the several branches of the U.S.P.H.S.

Government officials occasionally wish to discuss problems of medical care or public health with us.

Recently, representatives of the Civil Aeronautics Administration sought advice relative to revising the physical requirements demanded of applicants for a pilot's license. There is general agreement among the members of the Administration that an applicant for a license to fly commercially should pass a rigorous examination, but they are not agreed that an applicant who wishes to fly his own plane only should be required to pass the same examination, as one who aims to fly commercial planes. More time is required to learn to fly a plane than to operate an automobile and in this learning period physical weakness in the

applicant is likely to be discovered and reported by the pilot giving the lessons; hence, if a student is passed by his pilot, it may be assumed he can be considered physically fit at least to fly his own plane. No decision has been reached on this point as yet by the Commission.

The medical staffs of the Army, Navy and Veterans' Administration seek assistance in problems of public relations arising from their contacts with civilian members of the profession. A most annoying problem before the Veterans' Administration at present is—how to guarantee the veterans topnotch care in those states where chiropractors are licensed and insist upon being included in the treatment program.

This problem is most complicated in eleven states, where schools teaching chiropractic have been approved by the proper authorities for cooperation in the Veterans' Education Program. Not one of these schools, so far as we are informed, is a part of any recognized educational institution. They are all commercially conducted. However, approval by the state's agency gives them a status which will justify their graduates in seeking licensure to practice in the state, and also authority to partake in the Government program for providing medical care for veterans. It will be very difficult, because of the emotional aspect, for other states, where chiropractors are not licensed to practice, to deny these veterans the right to practice in their jurisdictions, if they seek it. Chiropractic seems to have achieved a legal status without scientific justification.

Leading labor unions have their headquarters in Washington, and we have been invited to conferences when they have medical matters under consideration. Just recently we have assisted Doctor Martin, of the Council on Medical Service, in arranging conferences with representatives of the United Mine Workers Union regarding improvement in the medical service rendered miners in the bituminous coal region.

Senator Byrd, several years ago, conducted a survey of the Government Departments, Bureaus and Ageneies and reported finding thirty-four of them carrying, in their annual budgets, some appropriation for health work. Since then, a few have abandoned their health activities but most persist. We are gradually informing ourselves of the activities conducted with those various funds.

The Congress, this year, authorized the appointment of a Commission to make an investigation of the various bureaus, divisions and agencies of the Executive Department of the Government, for the purpose of ascertaining the extent to which overlapping of funds and activities occur and, within the last month, Pres. Truman has announced the personnel of the Commission. It is to be headed by Ex-President Hoover, who has temporarily established his residence in Washington so as to give the work his full attention.

The correspondence of the office is very heavy during the time the Congress is in session. We have many inquiries from state, county and auxiliary society legislative chairmen for information concerning reported bills and for copies of bills or reports. Communications, in the form of suggestions and requests for information or material, are very welcome and with rare exception acknowledged and supplied on the day received. Also, answering the telephone calls, both local and long distance, absorbs a good part of every day.

Physicians visiting Washington usually call at the office either to visit or for assistance. Physicians are invited to make it their headquarters and avail themselves of its facilities.

The Washington Office aims to be a source of information and a liaison between the Congress and the profession; and, in order to accomplish this aim, it was deemed wise to register under the Lobbying Act. There are more than twenty agencies and individuals registered under the Act as interested in legislation relating to health activities. This is not the largest lobby, but it is significant of the interest health legislation commands throughout the country. Most of these representatives have established permanent offices in the city.

And now—a word with regard to the legislation we are following. Of the 7,289 (2108 S.—5181 H. R.) bills and resolutions introduced in the two Houses of this, the 80th Congress, 132 (51 S.—81 H. R.) were selected as of interest to our profession. Of this number, only fifty-six were advanced to the stage of hearings, and forty of these were reported out of committee to their respective chambers for passage, of which eight were passed by both Houses and have become a part of our Public Laws except for one (S. 526) which was vetoed by the President. Those not acted upon, either by the reference committees or by the respective Houses, may be taken up by the Congress when it reconvenes in January.

A bill (S. 140) which would create a Department of Health, Education and Security with Cabinet stature reached the floor of the Senate, but was not debated before the Senate recessed. This bill, after further amendment, may be enacted. Hearings were in progress on the Senate side, on the two medical service bills (S. 545—S. 1320). They will be concluded in the next session and the committee will decide upon some course of action in their regard. Several other highly socialistic bills demanding our very close watch are:

S. 1679—Broaden Social Security—Murray.

S. 1714—Maternal and Child Health Services—Pepper.

S. 1734—Unemployment Cash Sick Benefits—Murray.

H. R. 1980—Medical Care for School Children—Howell.

The 64 dollar question is: Will this Congress pass a compulsory health insurance bill? Your guess is probably as good as any other, but it can be safely said that it will not pass any of the present bills in the form they are now.

Adequate medical care is of such undisputed importance that Congressmen will consider any plan that promises to make it more available to the entire population. The feeling seems to be extending that if voluntary prepayment plans can do the work, they should be given the opportunity. At any rate, there seems to be unanimous agreement that any medical service plan will function best when organized on a state or community basis.

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LOUISIANA STATE MEDICAL SOCIETY NEWS

CALENDAR

PARISH AND DISTRICT MEDICAL SOCIETY MEETINGS

Society	Date	Place
East Baton Rouge	Second Wednesday of every month	Baton Rouge
Morehouse	Second Tuesday of every month	Bastrop
Orleans	Second Monday of every month	New Orleans
Ouachita	First Thursday of very month	Monroe
Rapides	First Monday of every month	Alexandria
Sabine	First Wednesday of every month	
Second District	Third Thursday of every month	
Shreveport	First Tuesday of every month	Shreveport
Vernon	First Thursday of every month	

SECOND DISTRICT MEDICAL SOCIETY

On Thursday, October 16 a group of New Orleans physicians who have participated in programs of the Second District Medical Society and have been honored by that group, were hosts to members of the District Society and their wives at a dinner at Antoine's. All present had a most enjoyable time and it is felt that Dr. Edmund Connely, who arranged for the dinner, and Dr. J. T. O'Ferrall, who presided on the occasion, should be congratulated on the pleasant evening furnished. Similar dinners have been given in past years and by the interest manifested should be continued in the future.

SEVENTH DISTRICT MEDICAL SOCIETY

On September 20 the annual fall conference of the medical society of the Seventh Congressional District was held in Lake Charles. The program for this conference was outstanding with such men

as Dr. Walter Grady Reddick, Dr. O. B. Gober, Dr. Hampton C. Robinson, Dr. Arild E. Hansen, and Dr. Marvin P. Knight, all of Texas, participating. In addition Dr. Champ Lyons spoke on "Management of Thermal Burns", Dr. Richard W. Vincent on "Plastic Surgery in Treatment of Burns", Dr. Joseph S. D'Antoni on "Diagnosis and Treatment of Amebiasis", Dr. John Adriani on "Obstetrical Anesthesia with Special Emphasis on Saddle and Spinal Anesthesia" and Dr. Conrad G. Collins on "Ovarian Pathology and Indications for Surgical Intervention". The meeting was presided over by Dr. J. J. Stagg, Jr., President of the Seventh District Society and Dr. J. Y. Garber, President of the Calcasieu Parish Medical Society, extended greetings to members and guests present.

At an informal dinner held at the Lake Charles Country Club Dr. Gilbert C. Anderson, President of the State Society, gave an address and brief talks were made by Dr. P. H. Jones, First Vice-President of the State Society, and Dr. Claude Martin, Councilor of the Seventh District.

The committees on arrangement for this meeting are indeed to be commended for the excellent program planned. It is very seldom that so many outstanding speakers are secured for a one day meeting and it is felt that all in attendance profited a great deal from a scientific standpoint and had a most enjoyable time socially.

It would no doubt be well for other district societies in the state to follow the example set by the Seventh District Society in having an annual conference of this type.

LAFOURCHE VALLEY MEDICAL SOCIETY

A meeting of the Lafourche Valley Medical Society was held at Grand Isle on September 13 and 14. This meeting included a scientific program, a dinner and other social activities and was greatly enjoyed by all present. It is hoped that the doctors of this section who failed to attend will be able to do so when another such opportunity is presented.

WASHINGTON PARISH MEDICAL SOCIETY

The Washington Parish Medical Society was recently reorganized at a meeting held for this purpose in Bogalusa. Dr. R. R. Ward was elected president of the group, Dr. R. D. Fornea, vice-president and Dr. C. W. Crain, secretary.

WEBSTER PARISH MEDICAL SOCIETY

At a meeting of the Webster Parish Medical Society, held in Minden on September 30, Dr. C. R. Reed, Jr., of Shreveport, gave a talk on "Diagnosis and Treatment of Cervical Fractures and Dislocations". Dr. J. P. Sanders, also of Shreveport, addressed the group outlining the aims and purposes of the American Academy of General Practice.

PARISH MEETINGS OF LOUISIANA FARM BUREAU

Members of the State Society are urged to attend meetings which are called by the Louisiana Farm Bureau in various parishes throughout the state for discussion of medical service for rural areas. Our cooperation has been requested and unless physicians are alert and actively interested in this subject there may be an attempt by some agencies toward socialization of this type of practice.

BURCH TO HEAD TULANE DEPARTMENT OF MEDICINE

Dr. George Edward Burch, associate professor of clinical and experimental medicine in the School of Medicine at Tulane University, has been appointed Chairman of the Department of Medicine and professor of medicine at the University, to succeed Dr. John H. Musser who served as head of the Tulane Medical Department for the past 23 years.

Dr. Burch is a native of Edgard, Louisiana and graduated from the Tulane Medical School in 1933 receiving his Master of Science degree from the University in 1934. In 1935 he was appointed instructor of medicine at Tulane and was named associate professor of medicine in 1943.

Research in the use of radio-active tracers in heart diseases earned for Dr. Burch the American Medical Association's gold medal award for the most original exhibit at the annual meeting held in Atlantic City last June. The exhibit illustrated the use of radio-active sodium in the study of congestive heart failure.

Formerly on the staff of the hospital of the Rockefeller Institute for Medical Research and consultant in medicine (cardiovascular) to the Surgeon General of the United States Army, Dr. Burch is at present senior visiting physician at Touro Infirmary and Charity Hospital in New Orleans. He is also consultant in cardiovascular diseases at Ochsner Clinic.

The Louisiana State Medical Society wishes to extend to the Tulane University and to Dr. Burch its felicitations on this appointment.

Dr. Roy Carl Young, of Covington, presented a paper on "Clinical Observations on the Treatment of the Alcoholic" at the Southern Psychiatric Association Meeting in Birmingham, on October 13 and 14.

SOUTHERN MEDICAL ASSOCIATION MEETING

The 1947 meeting of the Southern Medical Association to be held in Baltimore November 24-26 will no doubt be one of the most interesting and profitable meetings held by this organization. The meeting this year will be concentrated into three

days instead of three and one-half. Registration will open Monday morning, November 24 and the scientific program for that day will be conducted by the local profession. Meetings of the 21 sections of the Association will be held on Tuesday and Wednesday, November 25 and 26. Following is synopsis of the clinical sessions and sections for this meeting:

Monday, November 24. Forenoon and afternoon —General Clinical Sessions, Baltimore Day, medicine, surgery, and ophthalmology and otolaryngology, presentations by physicians of Baltimore. A General Public Session will be held at the Lyric Theater on Monday evening.

Tuesday, November 25. Forenoon—Section on Gastroenterology, Section in Neurology and Psychiatry, Section on Orthopedic and Traumatic Surgery, Section on Urology, Section on Industrial Medicine and Surgery, and Section on Medical Education. Afternoon—Section on Medicine, Section on Ophthalmology and Otolaryngology, Section on Surgery, Section on Obstetrics, Section on Physical Medicine, and Section on Public Health. A General Public Session featuring the address of the President followed by the President's Reception and Ball will be at the Lord Baltimore Hotel on Tuesday evening.

Wednesday, November 26. Forenoon—Section on Pediatrics, Section on Dermatology, Section on Radiology, Section on Gynecology, and Section on Anesthesiology. Afternoon—Section on General Practice, Section on Allergy, Section on Pathology, Section on Proctology, and Section on Ophthalmology and Otolaryngology.

ALLERGISTS TO MEET

The American Academy of Allergy will hold its annual convention at Hotel Jefferson, St. Louis, Missouri, December 15-17 inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy by registering without payment of fee. The program, the scientific and technical exhibits have been arranged to cover a wide variety of conditions where allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as the results of investigation and research. Round table conferences will be held on Monday afternoon, December 15. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Charles H. Eyermann, M. D., 634 North Grand Boulevard, St. Louis, Missouri.

RADIOLOGICAL SOCIETY OF NORTH AMERICA

The thirty-third annual meeting of the Radiological Society of North America will be held at the Hotel Statler in Boston, November 30-December 5. The meeting will open with registration on Sunday and the general session on Monday will include a symposium on the Economics of Medicine. Numerous papers pertaining to the latest advances in x-ray diagnosis and treatment will be delivered by members of the society each afternoon. On Wednesday morning symposia on pediatric roentgenology and on radioactive iodine, which is used in the treatment of certain thyroid conditions, will be held.

AMERICAN COLLEGE OF SURGEONS

The following members of the Louisiana State Medical Society were accepted into fellowship of the American College of Surgeons at the thirty-third convocation of the College held in New York on September 12: Drs. John A. Colclough, Daniel W. Goldman, Alfred B. Longacre, Melvin D. Steiner and Max Suter; all of New Orleans.

HOMETOWN MEDICAL CARE PLAN FOR VETERANS

On November 6, just preceding the secretaries and editors conference in Chicago there will be held by the A. M. A. a session for discussion of the Hometown Medical Care Plan for Veterans at present in effect in many states. At this meeting will be considered the questions of How is the plan working?; What are the difficult problems involved?; and Where and why should changes be made in the program?

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 6, 1948 at 2:00 p. m. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year.

A number of changes in Board regulations and requirements were put into effect at the last annual meeting of the Board held in Pittsburgh, Pennsylvania, from June 1 to June 7, 1947. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in ranks lower than Chief or Senior Staff of hospitals, or Associate Professorship in Schools of Medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences which involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months regardless of the duration of the course.

Applications are now being received for the 1948 examinations. Closing date for these applications will be November 1, 1947.

For further information and application blanks

address: Paul Titus, M. D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

INFORMATION NEEDED FOR A. M. A. DIRECTORY

Preparations are now being made to publish the new, Eighteenth Edition of the American Medical Directory. The last edition of the Directory was issued late in 1942. Since that time, it has been impossible to publish a new edition because of wartime restrictions and the shortage of paper and labor.

About November 15, a directory card will be mailed to every physician in the United States, its dependencies, and Canada, requesting information to be used in compiling the new Directory. Physicians receiving an information card should fill it out and return it promptly whether or not any change has occurred in any of the points on which information is requested. It is urged that those physicians also fill out the right half of the card, which information will be used exclusively for statistical purposes. Even if a physician has sent in similar information recently, mail the card promptly to insure the accurate listing of his name and address. There is no charge for publishing the data nor are physicians obligated in any way.

The Directory is one of the most important contributions of the American Medical Association to the work of the medical profession in the United States. In it, as in no other published directory, one may find dependable data concerning physicians, hospitals, medical organizations and activities. It provides full information on medical schools, specialization in the fields of medical practice, memberships in special medical societies, tabulation of medical journals and libraries, and, indeed, practically every important fact concerning the medical profession in which anyone might possibly be interested.

Therefore, should any physician fail to receive one of these Directory Information cards by December 1, he should write at once to the Directory Department requesting a duplicate card be mailed.

PRESENT DEMAND FOR NURSES

The American Nurses' Association has recently issued a statement concerning the present shortage of nurses and has proposed a program to attempt to remedy this situation. The Association "with all its resources, pledges itself to work to the limit in initiating and furthering activities to cope with this situation", according to the statement. It is gratifying to know of this activity and also to know that a special committee from the American Medical Association has been appointed to consider this subject. With such combined efforts it is hoped that this crisis may be relieved.

MOTION PICTURE FILMS

To assure the listing of all outstanding medical and surgical motion picture films in the revised "Catalogue of Professional Motion Picture Films" now being compiled by the Academy-International of Medicine, all film authors are urgently requested to write immediately for film questionnaires to be filled out and returned. Such requests should be addressed to the Academy-International of Medicine, 214 West Sixth Street, Topeka, Kansas.

MARKLE FOUNDATION POST-FELLOWSHIP GRANTS

Two hundred and fifty thousand dollars has been made available annually for five-year post-fellowship grants beginning 1948-49 by the John and Mary R. Markle Foundation. The purpose of the program is to attract much-needed talent to academic medicine by giving promising young scientists academic security and financial assistance for a period up to five years. The program will be conducted in cooperation with accredited medical schools in the United States and Canada and further details may be secured from the deans of such schools.

BENEFIT SHOE FOUNDATION

The Bristol Manufacturing Corporation, through its department of Christian Relations, has begun operation of the Benefit Shoe Foundation. This is a non-profit corporation offering single shoes and odd pairs at cost for amputees, paraplegics and others with mismated feet. For further information communicate with the National Foundation for Infantile Paralysis, 120 Broadway, New York City.

LESLIE DANA MEDAL

The award made annually for outstanding achievements in the prevention of blindness and the conservation of vision, by the National Society for the Prevention of Blindness, will be presented this year to Dr. Frederick H. Verhoeff, of Boston.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION 1948 AWARD CONTEST

The National Gastroenterological Association has announced its Annual Cash Prize Award Contest for 1948. One hundred dollars and a Certificate of Merit will be given for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The winning contribution will be selected by a board of impartial judges and the award is to be

made at the Annual Convention Banquet of the National Gastroenterological Association in June of 1948.

Certificates awarded to other physicians will be mailed to them. The decision of the judges will be final. The Association reserves the exclusive right of publishing the winning contribution, and those receiving certificates of merit, in its official publication, Review of Gastroenterology.

All entries for the 1948 prize should be limited to 5,000 words, be typewritten in English, prepared in manuscript form, submitted in five copies, accompanied by an entry letter, and must be received not later than April 1, 1948. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23, N. Y.

UROLOGY AWARD

The American Urological Association offers an annual award of $1000.00 (first prize of $500.00, second prize $300.00 and third prize $200.00) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Boston, Massachusetts, May 17-20, 1948.

For full particulars write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee. Essays must be in his hands before March 1, 1948.

ALVARENGA AWARD

In recognition of his studies on the evaluation of BCG vaccine in the control of tuberculosis the College of Physicians awarded on July 14, the Alvarenga Prize for this year to Dr. Joseph Aronson, of the United States Bureau of Indian Affairs.

The Alvarenga Prize was established by the will of Pedro Francisco daCosta Alvarenga of Lisbon, Portugal, an Associate Fellow of the College of Physicians, to be awarded annually by the College of Physicians on each anniversary of the death of the testator, July 14, 1883.

The College usually makes this award for outstanding work and invites the recipient to deliver an Alvarenga Lecture before the College.

ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Toronto, Canada, May 6th, 7th, 8th, 1948 providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than February 1st, 1948. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association. This will not prevent its further publication, however, in any Journal selected by the author.

CANCER CONFERENCE

The Southwest Regional Cancer Conference will be held in Fort Worth on November 20 at the Blackstone Hotel. This conference will be held under the auspices of the American Cancer Society and in cooperation with the Texas Division of the American Cancer Society. The one-day meeting will consist of morning and afternoon lecture sessions followed by open forum question and answer periods, a clinical luncheon and a public meeting in the evening. Further information about the conference may be secured from the Tarrant County Medical Society, 209 Medical Arts Building, Fort Worth 2.

HEALTH OF NEW ORLEANS

The Bureau of the Census, Department of Commerce, from the figures reported by the New Orleans Health Department, announces that there were reported in the City of New Orleans 133 deaths during the week which ended September 6. Eighty-eight of these deaths occurred in the white population and 45 in the negro with 19 in children under one year of age; 14 colored and five white. An increase in number of deaths reported is noted for the week which ended September 13. There were 97 white people who expired this week and 65 colored, six of the former and seven of the latter occurring in infants under one year of age. The report for the week ending September 20 showed a slight decrease in the total number of deaths, this being 153, divided 101 white and 52 nonwhite. The infant deaths, however, increased to 26, an equal number occurring in the white and colored. There were 59 fewer people who died in the city during the week ending September 27 than for the previous week; 58 white and 36 colored and only ten of these occurred in infants. The report for October 4 showed a total of 111 deaths including 13 infant deaths.

INFECTIOUS DISEASES IN LOUISIANA

The weekly morbidity report for the State of Louisiana for the week ending August 30 indicated that there were 46 new cases of cancer occurring in the state this week. The only other diseases reported in numbers greater than ten were pulmonary tuberculosis with 27 cases and unclassified pneumonia with 24. Meningococcus meningitis occurred in one instance in Vermilion Parish and there was one case of poliomyelitis reported from St. Martin Parish. Pulmonary tuberculosis led other reported diseases in incidence the next week as shown by the report for the week ending September 6. There were 78 cases of this disease reported followed by 30 cases of cancer, 23 each of malaria and unclassified pneumonia, 11 cases of whooping cough and 10 cases of septic sore throat. Twenty-two of the malaria cases occurred in Jackson Parish and one in Orleans. One case of poliomyelitis was reported from Lafourche Parish. There was a decrease in number of pulmonary tuberculosis cases reported for the week ending September 13, there being 60 listed. This was closely followed by 59 cases of cancer. Whooping cough with 15 cases, unclassified pneumonia with 12 and measles with 10, were the only other diseases reported in numbers of ten or more. There were no cases of poliomyelitis reported this particular week, however one case of meningococcus meningitis occurred in Orleans Parish and one in Webster Parish. Cancer and pulmonary tuberculosis were still the most prevalent diseases in the state according to the report of September 20. There were 30 cases of cancer and 13 of pulmonary tuberculosis reported this week and no other diseases were reported in numbers larger than ten. Two cases of meningococcus meningitis were reported; one from Franklin and one from Orleans Parish.

MONTHLY MORBIDITY FOR VENEREAL DISEASES
STATE OF LOUISIANA

Month Ending August 31, 1947

	Total This Month	Total Previous Months	Total to Date 1947
Chancroid	61	372	433
Gonorrhea	1276	8764	10040
Granuloma Inguinale	18	123	141
Lymphopathia Venereum	8	54	62
Syphilis	922	6757	7679

WOMAN'S AUXILIARY, LOUISIANA STATE MEDICAL SOCIETY

Honor was conferred on the Woman's Auxiliary to the Louisiana State Medical Society when at the annual meeting of the Woman's Auxiliary to the American Medical Association held in Atlantic City, June 9-12, Mrs. Arthur A. Herold of Shreveport, was elected and installed as Treasurer for the year 1947-48. Mrs. Herold has a most enviable record for length of service to the Woman's Auxiliary. She has held the following chairmanships: legislative chairman for four years, 1931-1932, and 1938-1941; director for three years, 1934-1936, and 1946-1947, resigning as director for 1947-1948 to accept the arduous duties of the office of treasurer; constitutional secretary, 1944-1946, being the first member to serve in this office under the new constitution and by-laws; and chairman of the resolutions committee, 1941-1942. Mrs. Herold has served as a member of many committees during the time that she has been a member of the Board of Directors and has attended annual meetings, conferences and Board meetings regularly.

Mrs. Herold has been an active member of the Woman's Auxiliary for many years. She was president of the Caddo Parish Auxiliary in 1928, and organized the Woman's Auxiliary to the Louisiana State Medical Society in 1929, serving first as its vice-president and the following year as president. She has been active in both her parish and state auxiliaries since that time. In 1933-1934, Mrs. Herold was president of the Woman's Auxiliary to the Southern Medical Association.

Mrs. Herold has held various offices in civic, educational and philanthropic organizations, and during the war was chairman of the Home Front Committee of the O. C. D. in Shreveport and of a Surgical Dressing group of the Red Cross. She has been president of the Woman's Department Club of Shreveport and has served as legislative chairman of the state and local branches of the American Association of University Women. For three years she has been Commander of the Field Army of the American Cancer Society, Caddo Parish.

We congratulate the Auxiliary to the American Medical Association for having a woman of Mrs. Herold's ability to serve as treasurer. Mrs. Herold is very highly regarded for her accomplishments and greatly loved for her gracious and charming personality by our State Auxiliary.

Mrs. Herold recommends two books that won the Norton Medical Award and should be of special interest to the wives of physicians: THE DOCTOR'S JOB—1945 by Carl Binger, M. D., and A SURGEON'S DOMAIN—1947 by Bertram M. Bernheim, M. D. The Norton Medical Award was established to encourage the writing of books for laymen by physicians or other professional workers.

CORRECTION

In the list of officers of the Woman's Auxiliary, carried in the October issue of the Journal the address of the Third Vice-President, Mrs. J. Eugene Toups was listed as 1956 Cloverdale Ave., Shreveport. The street address is correct, however the city should have been Baton Rouge.

BOOK REVIEWS

Roentgen Interpretation: By George W. Holmes, M. D. and Lawrence L. Robbins, M. D. 7th ed. rev. Philadelphia, Lea and Febiger, 1947. Pp. 398. Price, $7.00.

This is the seventh edition of an excellent text which has retained its position as the outstanding concise and comprehensive work on roentgen interpretation since the first edition in 1919. There are very few radiologists and teachers of radiology who are not thoroughly familiar with the book.

Dr. Lawrence Robbins has replaced Dr. Ruggles and the authors have attempted to keep the character of the book unchanged. This edition represents the first step in the gradual replacement of the positive prints of previous editions by negative illustrations. The subject matter has been thoroughly revised and brought up to date.

The text consists of an introduction and eleven chapters.

Chapter I deals with the many shadows and artefacts, which may cause confusion in interpretation. Of equal importance and as capably handled is the text of the second chapter pertaining to anatomical variations and development.

Chapter III on fractures and dislocations is of necessity short but the most frequent types of fractures are covered. Chapter IV is devoted to diseases of bone, Chapter V to the skull, Chapter VI to the spine and Chapter VII to joints, tendons and bursae. The chest, gastro-intestinal and genito-urinary tracts are discussed in Chapters VIII, IX and X respectively.

The last chapter on fluoroscopy, is especially valuable with the increased use of this diagnostic method. The statements regarding protection in fluoroscopy are timely and should be recognized as important by all who attempt this procedure.

As in the previous editions the text is clear and concise and in spite of its brevity the fundamentals of roentgen diagnosis are covered. The selection of illustrative roentgenograms is very good.

J. N. ANÉ, M. D.

A Manual of Otology, Rhinology and Laryngology: By Howard Charles Ballenger, M. D., F. A. C. S. 3rd ed. enl. and rev. Philadelphia, Lea & Febiger, 1947. Pp. 352, illus. pl. Price, $4.50.

This is one of the latest of many manuals on this subject. In three hundred and forty-six pages, 135 illustrations and 3 color prints the author has given a very concise and comprehensive brief of the subject. The book seems well suited for residents and those wanting a manual of disease and treatment of the ear, nose and throat.

Therapy is especially good, being up to date, concise and practical, something many of the other books have lacked.

The chapters dealing with hay fever and allergy and that on headaches and neuralgias are very good and form a comprehensive working basis in dealing with these conditions.

The section on diseases of the ear brings up to date and in concise form a subject that is more or less at the cross roads in this day of chemotherapy.

This manual is well recommended as a reference book for otolaryngological residents, post-graduate students and as a modern reference in the office.

MERCER G. LYNCH, M. D.

Histopathology of the Ear, Nose and Throat: By Andrew A. Eggston, B. S., M. D. and Dorothy Wolff, A. B., M. A. Ph. D. Baltimore, The Williams & Wilkins Co., 1947. Pp. 1080, illus. pl. Price, $18.00.

This is a welcome book to the otolaryngologist. For many years there has been talk of the need of such a book and rightly so for few textbooks of pathology give much time or space to ear, nose and throat pathology. In this book of 1080 pages beautifully illustrated, the authors have comprehensively covered the subject matter in a style which makes for easy reading. The illustrations are well grouped and spaced, as to be easily referred to, and very clear in their descriptions.

This is a book well recommended as an adjunct to every otolaryngologist's library, as well as that of the general pathologist. This is the first book of its kind to be published and marks another milestone in the progress of this specialty.

MERCER G. LYNCH, M. D.

The Pharmacopoeia of the United States of America: Thirteenth Revision (U. S. P. XIII). Easton, Pennsylvania, Mack Publishing Company, 1947. Pp. 957, illus. Price, $8.00.

The thirteenth revision of the Pharmacopoeia of the United States which became official April 1, 1947, marks another milestone in the history of this publication which first appeared in 1820. Although the pharmacopoeia is more widely circulated in the profession of pharmacy than among physicians, the latter receive no small benefit from the labor involved in each new edition. The drugs admitted to the pharmacopoeia are therapeutic agents which reflect the best medical knowledge of the day. Their choice involves the retaining of time-tested remedies of previous revisions or their replacement by more effective agents which have been adequately tested from the standpoint of therapeutic action and safety. With the rapid advances in therapy on the one hand and the plethora of new drugs and preparations on the other the pharmacopoeia is of value to the physician as a guide for the wise selection of therapeutic

agents. The pharmacopoeia is legally authorized to designate standards of potency and properties of the included preparations, a service which is usually taken for granted by those prescribing and using drugs. The regular revisions are now appearing at five year rather than at ten year intervals which was formerly the case. Furthermore in order to keep in step with recent rapid developments it has been necessary to adopt a continuous revision by issuing supplements as occasion requires.

The general character of the information supplied by the pharmacopoeia is essentially the same as in the past. It is not a text on pharmacology or therapeutics in that no discussion of the action or therapeutic application of the drugs are included. A description of the physical and chemical properties of the drug is given with methods of indentification and assay. An average dosage is also included. Many preparations found in U. S. P. XII do not appear in U. S. P. XIII among which may be mentioned bismuth subnitrate, carbon tetrachloride, ergot and the fluid extract of ergot, reduced iron, mercuric bichloride, mercury with chalk, a number of the volatile oils, phenyl salicylate and sulfapyridine. On the other hand a lengthy list of drugs are included for the first time such as carbachol, digitoxin, helium, protamine zinc insulin injection, lanatoside C, metacholine chloride, papaverine hydrochloride, sulfamerazine and various preparations of penicillin. A further noteworthy change in this revision may also be mentioned. English titles of drugs occupy the leading position and determine the alphabetical arrangement, with the previous Latin titles relegated to a secondary position. The alphabetical arrangement also involves the grouping together of various preparations—(tinctures, emulsions, etc.), and dosage forms (capsules, tablets, injections, etc.) of the same drug, in contrast to their appearance at widely separated points in U. S. P. XII.

This new revision of the Pharmacopoeia of the United States definitely merits the attention of all those who prescribe drugs.

RALPH G. SMITH M. D.

Practical Emulsions: By H. Bennett. 2d ed. rev. Brooklyn, N. Y., Chemical Publishing Co., Inc., 1947. Pp. 568. Price, $8.50.

In this book emulsions are considered from the standpoint of the practical worker in contrast to theoretical treatises on the colloid and physicochemical aspects of the subject. The first part of the book is concerned with general information such as types of emulsions, emulsifying agents, methods of preparation and modern equipment. Chapters on stability and dispersing and wetting agents are also included. In this section of the book will be found a certain amount of theoretical as well as practical information on the above phases of the subject. The second section which is an innovation in this edition consists of a symposium on industrial emulsions written by authorities in various fields. Papers on lecithin, pectin, polyhydric alcohols and soaps as emulsifying agents are included. Of interest to the physician is a paper by Abraham Taub on surface active agents as germicides which deals with the action of such cationic agents as Zephiran Chloride, Phemerol and Ceepryn. It was of interest to the reviewer to learn that Domagk who was awarded the Nobel prize for his work on or in sulfonamides also initiated the technical development of these cationic agents as germicides. A further chapter in this section includes papers on cosmetics, dyes, paints, leather goods, foods, industrial waxes and synthetic rubber latex in many preparations of which emulsion formation is of primary importance. The third and most extensive part of the book consists of formulae for emulsions with brief directions for their preparation. These are classified by chapters according to use such as agricultural sprays, cleaners and soaps, cosmetics and drugs, food emulsions, medical emulsions, paints, polishes, etc. It is obvious that this book is of primary interest to those who are concerned with the manufacture or practical aspects of emulsions. From the standpoint of the physician the information with certain minor exceptions must be classified as "cultural."

RALPH G. SMITH, M. D.

PUBLICATIONS RECEIVED

The Commonwealth Fund, New York: The Practical Nurse, by Dorothy Deming, R. N.

J. B. Lippincott Company, Philadelphia: Handbook of Psychiatry, by Winfred Overholser, A. B., M. D., Sc. D. and Winifred V. Richmond, B. S., A. M., Ph. D.

C. V. Mosby Company, St. Louis: Synopsis of Obstetrics (3rd edition), by Jennings C. Litzenberg, B. Sc., M. D., F. A. C. S.; Communicable Diseases (2nd edition), by Franklin H. Top, A. B., M. D., M. P. H., F. A. C. P.

Grune & Stratton, New York: Epilepsy, by Paul H. Hoch, M. D. and Robert P. Knight, M. D.

Charles C. Thomas, Springfield, Illinois: Trichomonas Vaginalis and Trichomoniasis, by Ray E. Trussell, M. D.